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TETRAHEDRON: *ASYMMETRY*

Stereoselective synthesis of (+)-frontalin

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Abstract

Alkylation of the SAMP hydrazone of 1,3-dioxa-5-one provides a convenient way (8 steps, 40% overall yield) to synthesize frontalin in high optical purity (over 95%).

1. Introduction

Synthesis of chiral natural products in enantiomerically pure form is a topic of current interest and many reports describing new methodologies designed to achieve this goal and improvements in known synthetic methods appear every year. The most popular methods for construction of carbon–carbon bonds involve species having carbanionic character, with lithiated carbonyl compounds (ketones and esters) and their nitrogen derivatives (imines, enamines and hydrazones) being most common, and stereoselective variants of these methods are thus of primary importance. As part of our interest in developing enantioselective deprotonation methodology we have recently elaborated lithiation of 2-substituted-1,3-dioxa-5-ones with the intent to apply this reaction to the synthesis of oxygenated natural products.[1] Below, we describe a synthetic approach to frontalin (**1**), the aggregation pheromone of *Dendroctonus* beetles, based on Enders' SAMP/RAMP methodology.[2–4] This approach, which involves deprotonation of chiral hydrazones derived from dioxanones and thus can be treated as a method complementary to the enantioselective deprotonation, provided an easy access to frontalin and could, in a more general sense, be useful in the synthesis of other natural products of this type.[5]

2. Results and discussion

Our retrosynthetic analysis of frontalin (**1**) is shown in Scheme 1. The first transform (the deoxygenation transform) actually increases the molecular complexity in order to make the stereocenter at C-1

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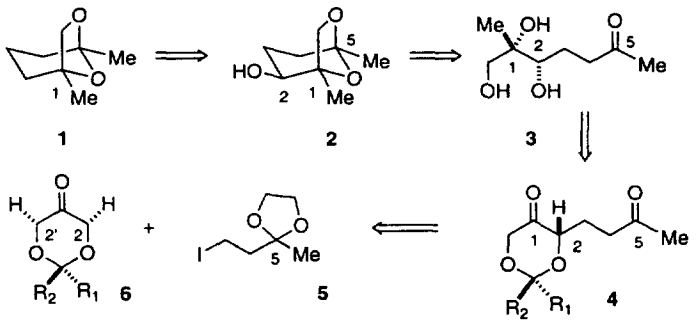
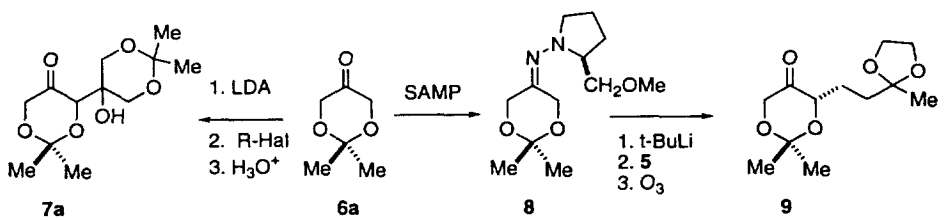
clearable.[6] Disconnection of the two C–O bonds in the acetal group leads to the ketone-triol **3**, which can be further simplified by the use of the Grignard addition transform to compound **4**, which has the diol functionality protected as a cyclic acetal. The Grignard transform was expected to be diastereoselective by virtue of the presence of the stereocenter at C-2. Finally, compound **4** was retrosynthetically reduced to the symmetrical dioxanone **6**. A selective construction of the stereocenter at C-2 is crucial to this strategy. It could be achieved via differentiation of the two enantiotopic axial hydrogens (enantioselective deprotonation)[7] at C-2 and C-2′ (frontalin numbering) in compound **6** (R_1 and R_2 different) or by using a chiral auxiliary and thus rendering the two hydrogens diastereotopic. We decided to try the former approach first.



Scheme 1.

We had previously described a convenient method of synthesis of dioxanones and some reactions of dioxanone lithium enolates.[1] Recently, we have also elaborated a protocol for efficient enantioselective deprotonation of these compounds,[8] and it was expected that alkylation of the lithium enolate derived from **6** using the appropriate alkyl halide **5** should provide a convenient entry point towards frontalin synthesis. However, we were unable to alkylate any of the lithiated dioxanones (several compounds with different R_1 and R_2 groups were tried) with alkyl halides. Even reactive alkyl halides like benzyl bromide or allyl bromide failed to react with dioxanone lithium enolates under a variety of conditions, contrary to a literature precedent.[9] In most cases the self aldol products e.g., **7a** were obtained (Scheme 2). In contrast, dioxanone enolates reacted readily with benzaldehyde, and other aldehydes, to produce the corresponding aldol products in high yields.[1] The failure of the alkylation reaction forced us to look for other methods.

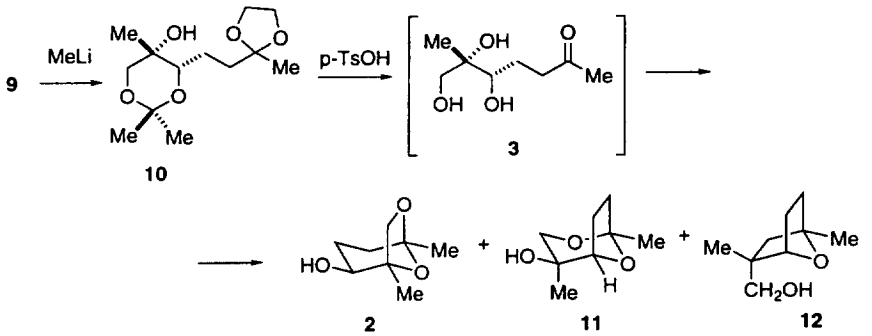


Scheme 2.

Amongst the methods relying on chiral auxiliaries to convert a symmetrical ketone into a chiral starting material, the SAMP/RAMP hydrazone method, developed by Enders, is well known for its efficiency.[2–4] We have decided to use this method to alleviate the alkylation problem; lithiated hydrazones are usually easy to alkylate. Towards this end compound **6a** was converted into the corresponding chiral hydrazone **8** using SAMP and the hydrazone was lithiated with t-BuLi, alkylated with the iodide **5** at −100°C, and the hydrazone moiety was then cleaved with ozone to yield the ketone **9** in 92% yield over 4 steps

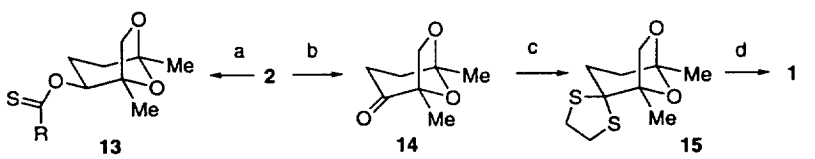
(Scheme 2). The absolute configuration at C-2 was assigned to be as drawn on the basis of the known reactivity of SAMP hydrazones of other ketones.[10]

The ketone **9** was then subjected to a nucleophilic addition using MeLi, the addition proceeded in 75% yield and selectively *trans* to the substituent at C-4 to give compound **10** and its epimer at C-5 in a 94:6 ratio (dioxanone numbering, Scheme 3). Addition of MeLi to **9** was deduced to be equatorial after analyzing the structure of compound **2** and from the sign of rotation of the final product (frontalin). Axial addition would have yielded a different stereoisomer of **2** (the mirror image of the epimer of **2** having the OH axial) and, ultimately, the levorotatory isomer of frontalin. At this stage we were able to measure the enantiomeric purity of compound **10** by ^{1}H-NMR and chiral shift reagents. A measurement using Eu(hfc)$_3$ revealed that compound **10** was produced in 95% ee. The two acetal groups were then hydrolyzed with para-toluenesulfonic acid. The resulting triol **3** could, in principle, undergo intramolecular acetalization under the reaction conditions to produce three different species **2**, **11** and **12**. The spectral data indicated that compound **2** was the major product and accounted for 97% of the product mixture. The structure of compound **2** was deduced from the NMR data — the spectra of the epimer of **2** (OH axial) have been published before.[11]



Scheme 3.

The hydroxyl group in compound **2** had to be removed to complete the synthesis of frontalin. Barton dehydroxylation[12,13] was tried first, but the yield of the free radical fragmentation step was low. Several thiocarbonyl derivatives of **2** (structure **13**, Scheme 4, R=MeS, imidazole, OC_6F_5; conditions: n-Bu_3SnH, AIBN, THF, diglyme or PhH) were used in combination with different solvents in an effort to optimize the conditions, however, the highest yield did not exceed 49%. Next, we investigated desulfurization of the ketone thioacetal **15** derived from **2** as a way to remove the OH group. Oxidation of the alcohol **2** with PDC proceeded smoothly to give the corresponding ketone **14**. Formation of the thioacetal **15** had been reported to be difficult[14] and it turned out that the choice of the Lewis acid for thiacetalization was critical. After some experimentation we observed that zinc triflate[15] worked well, and the thioacetal **15** was produced in good yield. Desulfurization was accomplished with Raney nickel[16] to give the dextrorotatory isomer of frontalin (**1**).



Reagents: a. n-BuLi, CS_2, MeI or C_6F_5OCSCl; b. PDC, CH_2Cl_2 (80% yield); c. $(CH_2SH)_2$; $Zn(OTf)_2$; CH_2Cl_2 (85% yield); d. RaNi (97% yield).

Scheme 4.

In summary, a synthesis of (+)-frontalin based on the stereoselective alkylation of the chiral SAMP derivative of 2,2-dimethyl-1,3-dioxa-5-one was accomplished in 8 steps in 40% overall yield. The levorotatory isomer could be obtained by using the corresponding RAMP derivative.

3. Experimental

3.1. General

All air sensitive reactions were carried out under nitrogen. Tetrahydrofuran and diethyl ether were distilled under nitrogen from sodium and benzophenone. Gas chromatography (GC) was performed using a Helwett Packard 5890A instrument fitted with a methyl silicone gum column (HP-1, 5 m×0.53 mm). Chromatogtraphy was carried out using Merck silica gel 60 (230–400 mesh) or Sigma silica gel Type H (10–40 μm). Concentrated phosphate buffer, used frequently to quench reactions, was prepared by dissolving sodium hydrogen phosphate (47 g) and sodium dihydrogen phosphate (32 g) in water (0.5 l).

Melting points and boiling points are uncorrected. Optical rotations were measured on a Perkin–Elmer 241 polarimeter, all concentrations are given in g/100 ml. Proton magnetic resonance (^{1}H NMR) and carbon magnetic resonance (^{13}C NMR) spectra were recorded on a Bruker AM-300 (300 MHz) spectrometer in $CDCl_3$ solvent unless otherwise noted. Chemical shifts are reported in ppm units of δ scale, with TMS as the internal standard. Only diagnostic IR peak frequencies are reported. Mass spectra are reported as m/z ratios (relative intensity). Electron impact (EI) ionization was accomplished at 70 eV and chemical ionization (CI) at 50 eV. SAMP and t-BuLi were purchased from Aldrich and compound **5** was prepared from ethyl acetoacetate via a precedented 3 step procedure.[17,18]

3.2. (S)-1-(2,2-Dimethyl-1,3-dioxan-5-ylideneamino)-2-methoxymethylpyrrolidine 8

Compound **8** was synthesized according to a literature procedure.[4] 2,2-Dimethyl-1,3-dioxan-5-one (1.00 g, 7.68 mmol) was dissolved in benzene (25 ml) and (*S*)-(−)-1-amino-2-(methoxymethyl)pyrrolidine (1.00 g, 7.68 mmol) was added. The solution was gently refluxed for 24 h and the evolving water was trapped with molecular sieves (4 Å) in a Soxhlet apparatus. After cooling to r.t. diethyl ether (100 ml) was added, and the solution was washed with water (2×5 ml) and dried with anhydrous magnesium sulfate. The solvent was removed and the remaining liquid was distilled in a Kugelrohr to afford compound **8** as a colorless oil (1.82 g, 99%). Properties: bp 150°C, 1 mm Hg (Kugelrohr); R_f 0.29 (hexane:ethyl acetate=2:1); $[\alpha]^{25}_D$ +238 (c 1.5, CH_2Cl_2), (lit.[4] $[\alpha]^{23}_D$ +230, neat).

3.3. (S)-2,2-Dimethyl-4-[2-(2-methyl-1,3-dioxolan-2-yl)ethyl]-1,3-dioxan-5-one 9

Hydrazone **8** (1.84 g, 7.66 mmol) was dissolved in THF (25 ml) and cooled to −78°C. Next, t-butyllithium (5.00 ml, 1.7 M solution in pentanes, 8.42 mmol) was added dropwise and the mixture was stirred for 1.5 h at −78°C. The metallated hydrazone solution was cooled to −100°C and the iodide **5** (neat, 2.038 g, 8.42 mmol) was added dropwise. After 1.0 h the solution was warmed to −78°C and was stirred at that temperature for 12 h. The mixture was warmed to r.t. and diethyl ether (200 ml) was added. The solution was then washed with a pH 7 buffer (1×15 ml) and brine (2×15 ml). Drying with anhydrous magnesium sulfate and removal of the solvent afforded the crude alkylated hydrazone. This compound was purified by chromatography (R_f 0.34, diethyl ether:pentane=2:1). The hydrazone was next dissolved in dichloromethane (150 ml) cooled down to −78°C and ozone was bubbled through the

solution. The excess ozone was removed with a stream of argon. The solution was warmed to r.t. and the solvent was evaporated. The remaining liquid was purified by chromatography (hexane:ethyl acetate=2:1) which afforded compound **9** as a colorless oil (1.751 g, 94%). Properties: ^{1}H NMR: 4.28–4.19 (m, 2H), 4.01–3.88 (m, 5H), 2.05–1.93 (m, 1H), 1.86–1.55 (m, 3H), 1.43 (s, 3H), 1.40 (s, 3H), 1.30 (s, 3H); ^{13}C NMR: 209.3, 109.7, 100.7, 74.4, 66.6, 64.7, 64.6, 34.2, 24.0, 23.8, 23.6, 23.2; IR: 2984, 2881, 1745, 1222, 1046 cm^{-1}; MS: (CI-NH_3) 245 (M+1, 26), 187 (21), 186 (12), 183 (15), 161 (29), 145 (24), 144 (10), 143 (100), 99 (10), 87 (76), 86 (15), 72 (16); anal. calcd for $C_{12}H_{20}O_5$: C, 59.00; H, 8.25. Found: C, 58.94; H, 8.41; $[\alpha]^{25}_D$ −197.1 (c 1.5, dichloromethane).

3.4. (4S,5S)-2,2,5-Trimethyl-4-[2-(2-methyl-1,3-dioxolan-2-yl)ethyl]-1,3-dioxan-5-ol **10**

Ketone **9** (7.464 g, 30.56 mmol) was dissolved in THF (250 ml). The solution was cooled to −78°C and methyllithium (32.70 ml, 1.4 M solution in diethyl ether, 45.84 mmol) was added. After 0.5 h the reaction mixture was warmed to 0°C and was kept at that temperature for another 0.5 h. The reaction was quenched with brine (25 ml) and the aqueous layer was extracted with diethyl ether (3×50 ml). The combined ether solutions were dried with anhydrous magnesium sulfate and the solvent was evaporated. The diastereoselectivity of methyllithium addition (94:6 at 94% conversion) was determined by GC. Chromatography (elution with increasing amounts of AcOEt in hexane up to hexane:AcOEt=1:2) afforded a colorless oil (5.966 g, 75%). The e.e. was measured by ^{1}H NMR using a chiral shift reagent (+)-Eu(hfc)$_3$ and was determined to be 95%. Properties: mp 47–50°C (diethyl ether); R_f 0.28 (hexane:ethyl acetate=1:1); $[\alpha]^{25}_D$ −15.3 (c 1.0, dichloromethane, 95% e.e.); ^{1}H NMR: 3.98–3.90 (m, 4H), 3.75 (d, *J*=12.0 Hz, 1H), 3.65–3.59 (m, 1H), 3.35 (d, *J*=12.0 Hz, 1H), 2.95 (s, 1H), 1.95–1.85 (m, 1H), 1.69–1.48 (m, 3H), 1.42 (s, 6H), 1.31 (s, 3H), 1.00 (s, 3H); ^{13}C NMR: 110.1, 98.9, 76.1, 70.4, 66.8, 64.6, 64.5, 34.9, 29.6, 23.8, 22.6, 18.9, 18.2; IR: 3502, 2984, 2872, 1372, 1061 cm^{-1}; MS: (EI) 245 (11), 145 (50), 116 (16), 101 (16), 87 (100), 83 (11), 72 (11), 59 (32); anal. calcd for $C_{13}H_{24}O_5$: C, 59.98; H, 9.29. Found: C, 59.77; H, 9.45.

3.5. (1R,2S,5S)-1,5-Dimethyl-6,8-dioxabicyclo[3.2.1]octan-2-ol **2**

Alcohol **10** (5.727 g, 22.00 mmol) was dissolved in CH_2Cl_2 (150 ml) and p-toluenesulphonic acid monohydrate (0.050 g, 0.26 mmol) was added. The solution was refluxed for 1 h and then was cooled to r.t. Three products were detected in the mixture by GC (97:1:1:1). Compound **2**, which was the major product, was purified by flash chromatography (elution with increasing amounts of AcOEt in hexane up to hexane:AcOEt=1:2). Distillation at 1 mmHg provided a colorless oil (3.028 g, 87%). Properties: bp 105–107°C at 1 mmHg; R_f 0.22 (hexane:ethyl acetate=1:1); $[\alpha]^{25}_D$ +41.2, (c 2.2, dichloromethane); ^{1}H NMR: 4.14 (d, *J*=7.5 Hz, 1H), 3.69–3.60 (m, 1H), 3.39 (dd, J_1=7.5, J_2=1.0 Hz, 1H), 1.97–1.89 (m, 2H), 1.80–1.60 (m, 3H), 1.42 (s, 3H), 1.36 (s, 3H); ^{13}C NMR: 107.1, 82.1, 71.1, 70.3, 36.0, 27.3, 23.7, 19.4.

3.6. (1S,5S)-1,5-Dimethyl-6,8-dioxabicyclo[3.2.1]octan-2-one **14**[5,14]

Compound **2** (0.474 g, 3.00 mmol) was dissolved in CH_2Cl_2 (50 ml) and pyridinium dichromate (1.129 g, 3.00 mmol) was added. The mixture was stirred for 48 h. Another portion of the oxidant (1.129 g, 3.00 mmol) was added and the reaction was stirred for another 48 h. After that time the GC showed 95% conversion. The reaction mixture was applied on a silica pad and the ketone was purified by chromatography (elution with increasing amounts of AcOEt in hexane up to hexane:ethyl acetate=1:1). The product **14** was a white solid (0.375 g, 80%). Properties: mp 53–55°C (Et_2O; lit.[5] 52.7–53.4°C); R_f

0.57 (hexane:ethyl acetate=1:1); $[\alpha]^{25}_D$ +58.0 (c 1.5, CH_2Cl_2) (lit.[5] $[\alpha]^{29}_D$ +62.39, [c 0.4, $CHCl_3$]); ^1H NMR: 3.96 (d, J=8.0 Hz, 1H), 3.60 (d, J=8.0 Hz, 1H), 2.63–2.41 (m, 2H), 2.22–2.14 (m, 2H), 1.58 (s, 3H), 1.40 (s, 3H). ^{13}C NMR: 206.5, 108.2, 84.8, 73.0, 36.6, 32.7, 24.0, 15.2.

3.7. *(1S,5S)-1,5-Dimethyl-2,2-(1,3-dithiolan-2-yl)-6,8-dioxabicyclo[3.2.1]octane* **15**[5]

The procedure was adopted from the literature report for a similar transformation.[15] Ketone **14** (0.375 g, 2.40 mmol) was dissolved in 1,2-dichloroethane (25 ml) and 1,2-ethanedithiol (0.25 ml, 3.00 mmol) was added, followed by addition of zinc(II) triflate (1.091 g, 3.00 mmol). The heterogeneous reaction mixture was stirred for 12 h. Filtration through a short silica column followed by chromatography (elution with increasing amounts of AcOEt in hexane up to the ratio of hexane:ethyl acetate=2:1) afforded the product as a white solid (0.473 g, 85%). Properties: mp 44–48°C (Et_2O); R_f 0.45 (hexane:ethyl acetate=4:1); $[\alpha]^{25}_D$ −10.4, (c 1.5, CH_2Cl_2), (lit.[5] $[\alpha]^{29}_D$ −7.82, [c 1.0, $CHCl_3$]); ^1H NMR: 4.06 (d, J=8.0 Hz, 1H), 3.63 (d, J=8.0 Hz, 1H), 3.40–3.28 (m, 2H), 3.26–3.11 (m, 2H), 2.45–2.32 (m, 1H), 2.18–2.08 (m, 1H), 1.99–1.86 (m, 1H), 1.84–1.75 (m, 1H), 1.60 (m, 3H), 1.45 (m, 3H); ^{13}C NMR: 108.3, 86.8, 74.4, 71.8, 40.1, 39.2, 38.0, 36.7, 23.8, 20.1.

3.8. *(+)-Frontalin*[5,19,20]

RaNi (20 g, 50% slurry in water) was washed with methanol (10×50 ml) and suspended in methanol (30 ml). Next, the solution of the thioacetal **15** (0.200 g, 0.86 mmol) in MeOH (1 ml) was added. The reaction mixture was stirred and refluxed for 15 min and then was cooled to 5°C. The solvent was next decanted and the remaining RaNi was washed with pentane (3×50 ml). The combined organic solutions were next washed with water (25 ml) and dried with anhydrous magnesium sulfate. The sample was concentrated using a rotovap (bath temperature 0°C) to a small volume (1 ml) and dichloroethane (5 ml) was added and the solvents were evaporated again. The product, a colorless oil, did not contain GC-detectable impurities (0.119 g, 97%). Properties: $[\alpha]^{25}_D$ +54.8, (c 1.5, diethyl ether), (lit.[20] $[\alpha]^{23}_D$ +54.4, [c 1.3, diethyl ether]); ^1H NMR: 3.91 (d, J=6.5 Hz, 1H), 3.45 (dd, J_1=6.5, J_2=1.5 Hz, 1H), 1.96–1.78 (m, 1H), 1.69–1.50 (m, 5H), 1.43 (s, 3H), 1.32 (s, 3H); ^{13}C NMR: 108.0, 80.0, 74.1, 34.5, 33.9, 24.6, 23.0, 18.0.

Acknowledgements

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