Large-Scale Preparation of Enantiomerically Pure (4a*R*)-(–)-1,4a-Dimethyl-4,4a,7,8-tetrahydronaphthalene-2,5(3*H*,6*H*)-dione: A Useful Wieland–Miescher Diketone Analogue

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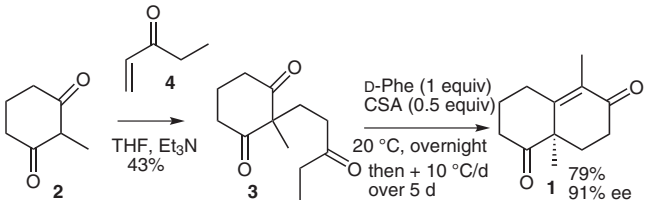
Abstract: Wieland–Miescher diketone analogue **1** is a widely used precursor for asymmetric synthesis of natural sesquiterpenes and diterpenes. We describe here a large-scale preparation (>125 g batches) of enantiomerically pure compound **1** starting from propionyl chloride and using very simple and cheap reagents. A new one-pot sequence to the intermediate 2-methylcyclohexane-1,3-dione is also described.

Key words: Wieland–Miescher diketone, Dieckmann condensation, thiomethylenation, preferential crystallization

Many total synthesis of natural compounds (mostly sesquiterpenes and diterpenes) starting from enantiomerically pure Wieland–Miescher diketone analogue **1** have been described.[1] Diketone **1** is generally prepared using the procedure published by Hagiwara and Uda in 1988 (Scheme 1).[2]



Scheme 1 Hagiwara–Uda synthesis of diketone **1**

These asymmetric cyclization conditions [DMF, CSA (0.5 equiv)] were first described in 1985 for the preparation of a diketone bearing an angular carbinol group,[3] and were slightly modified by Corey et al.[4] and Agami et al.[5] for the synthesis of analogues.

Despite a large number of applications, the Hagiwara–Uda procedure suffers from some drawbacks for a large-scale preparation and industrial uses of diketone **1**:

- the reaction mixture is diluted (only 15 g of diketone **1** can be prepared in a 2000 mL flask);

- the annulation requires long reaction times (4 to 5 days) and a careful control of reaction temperature (30–70 °C, 10 °C per day for 4 days); and

- the use of expensive ethyl vinyl ketone (**4**) and 2-methylcyclohexane-1,3-dione (**2**) as precursors.

Most total synthesis of natural compounds using **1** as enantiomerically pure starting material require an important number of steps, therefore the need to have **1** available in large quantity is mandatory. Our ongoing program directed towards gram-scale terpenoid synthesis from Wieland–Miescher ketone analogue **1** prompted us to investigate modified conditions that would deliver enantiomerically pure **1** from cheaper precursors in 100 g batches and in shorter time.

In 1984, a seemingly overlooked paper by Uma et al.[6] described the same asymmetric annulation under more drastic conditions (AcOH, 120 °C) leading to diketone **1** from **3** in only 2 hours in 80% yield and quite high enantiomeric excess (87%). These conditions considerably decreased the reaction time and allowed concentrations ten times higher than Hagiwara–Uda procedure (150 g of diketone **1** can be prepared in a 3000 mL flask).

In this work, we planned to use these annulation conditions from triketone **3** obtained by alkylation of the triethylammonium enolate of dione **2** with 1-chloropentan-3-one (**5**) as a cheaper and less toxic alternative to ethyl vinyl ketone (**4**). Actually, **5** can be prepared in large scale (>300 g/batch) from ethylene and propionyl chloride using conditions described by Heathcock et al.[7] Dione **2** is commercially available, but is quite expensive and its preparation from cyclohexane-1,3-dione by methylation of the corresponding enolate leads generally to low to modest yields (25–48%).[8] Considering that **5** is anyway an essential component in the synthesis of **1**, and that dione **2** itself might be obtained from 1-chloropentan-3-one (**5**) and diethyl malonate, we focused at first on an unprecedented one-pot synthesis of dione **2**. If successful, the planned synthetic sequence depicted in Scheme 2 would allow the large-scale (100 g batches) preparation of enantiomerically pure diketone **1** using only propionyl chloride and diethyl malonate as substrates and D-phenylalanine (D-Phe) as enantioselective organocatalyst under environment-friendly conditions and using only crystallizations for purifications.

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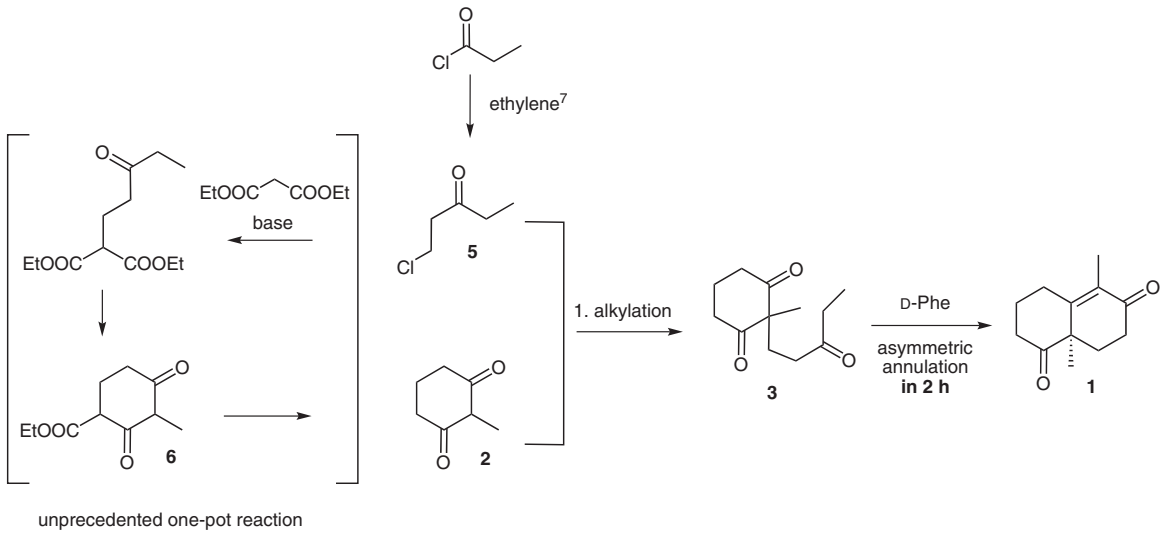
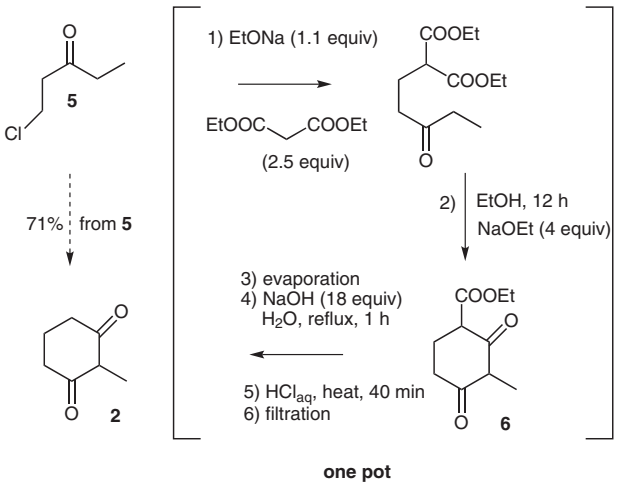


Scheme 2 Planned synthetic sequence for the preparation of **1** from propionyl chloride

One-Pot Synthesis of 2-Methylcyclohexane-1,3-dione (2)

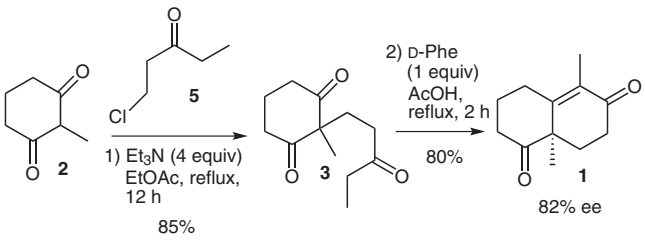
We prepared 1-chloropentan-3-one (**5**) from propionyl chloride and ethylene in the presence of aluminum trichloride in dichloromethane at 0 °C as described by Heathcock et al.[7] Batches of 350 g of material can be obtained in half a day. 1-Chloropentan-3-one (**5**) was treated with 2.5 equivalents of diethyl malonate in the presence of 1.1 equivalents of sodium ethoxide in ethanol for 20 hours. Excess of diethyl malonate was necessary to avoid dialkylation products. Four equivalents of sodium ethoxide were then added, resulting in a Dieckmann condensation to give the cyclic diketo ester **6**. Finally, evaporation of ethanol and basic hydrolysis followed by acidification–decarboxylation afforded the dione **2**, which was easily collected by filtration in pure and crystalline form in 71% overall yield (Scheme 3).



Scheme 3 One-pot preparation of dione **2** from **5**

Synthesis of Wieland–Miescher Diketone Analogue 1 from 2

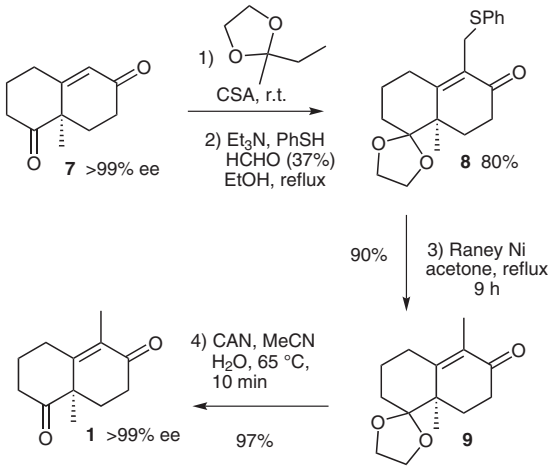
With dione **2** in our hands, we prepared the annulation precursor **3** using once again the 1-chloropentan-3-one (**5**) as alkylating reagent. Finally we applied the Uma et al.[6] protocol on triketone **3** and these conditions afforded in our hands the diketone **1** in 80% yield, but with only 82% ee (Scheme 4).



Scheme 4 Preparation of diketone **1**

Different recrystallization attempts from Et_2O–hexane as described by Cheung et al.[1q] did not deliver enantiomerically pure material in our hands.[9] Having in mind the purification procedure developed by Buchschacher et al.[10] to obtain enantiomerically pure Wieland–Miescher diketone **7** we decided to test a preferential crystallization and to seed the crude material with an enantiomerically pure crystal of **1**.

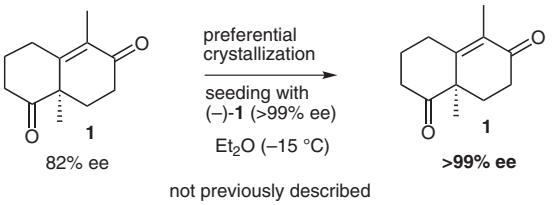
Despite the short way reported in the literature by Cheung et al.[1q] using Hagiwara–Uda protocol (Scheme 1) to obtain enantiomerically pure diketone **1**, our own disappointing experiences met with the enantiomeric purification of the Wieland–Miescher diketone **7** (ee ~75%) by means of simple crystallization, prompted us to develop a longer but more secure alternative. As we needed only small amounts of enantiomerically pure material **1**, we decided to homologate the Wieland–Miescher diketone **7**, which is commercially available in either enantiomeric form, as depicted in Scheme 5.



Scheme 5 Preparation of enantiomerically pure diketone **1** from Wieland–Miescher diketone **7**

The chemoselective protection[11] of one of the carbonyl groups as dioxolane followed by a Kirk–Petrow thiomethylenation[12] led to compound **8** in 80% overall yield. Classical reductive conditions using Raney Nickel in alcohols were ineffective on compound **8** and desulfenylation occurred in very good yields (90%) under more drastic conditions (Raney Ni, acetone, reflux).[13] Finally, deprotection[14] of the resulting product **9** afforded enantiomerically pure diketone **1** in excellent yield (97%).

One crystal of this compound was added to an ethereal solution of diketone **1** previously obtained in 82% optical purity to afford after preferential crystallization enantiomerically pure Wieland–Miescher analogue **1** in excellent yield (Scheme 6).



Scheme 6 Unprecedented preferential crystallization of diketone **1**

We have described a large-scale access to Wieland–Miescher diketone analogue **1**, a widely used precursor for asymmetric synthesis of terpenoids. With one crystal of enantiomerically pure material in hand and starting from propionyl chloride and very simple and cheap reagents, >125 g batches of compound **1** (ee >99%) can be prepared within one week via a one-pot preparation of dione **2** or from commercially available dione **2** within two days. A further advantage is that most of the solvents used (EtOAc, EtOH, AcOH) are both user- and environment-friendly.

Reagents and solvents (reagent grade) were used without further purification. THF was distilled over sodium benzophenone ketyl. CH_2Cl_2 was distilled over CaH_2. Abs EtOH was dried by distilling over Mg. Column chromatography: silica gel 60 (230–400 mesh, 0.040–0.063 mm) was purchased from E. Merck. TLC was performed on glass sheets coated with silica gel 60 F_{254} (otherwise stated) purchased from E. Merck; visualization by UV light or through staining with phosphomolybdic acid reagent. IR (cm^{-1}) measurements were performed using Universal ATR sampling accessories. NMR spectra (^1H and ^{13}C) were recorded on a 200 MHz or 300 MHz or 400 MHz. Chemical shifts are reported in ppm with the solvent ($CDCl_3$) resonance at $\delta = 7.26$ for ^1H spectra and $\delta = 77.0$ for ^{13}C spectra. Optical rotations were measured on a polarimeter with a sodium lamp. The enantiomeric excess (ee) of the product (–)-**1** was determined by ^1H NMR spectroscopy at 400 MHz with $Eu(tfc)_3$ versus racemic compound. The mass spectra were performed at 70 eV; mass range 35–400.

Compounds **3**, **5**, and **8** were prepared according to literature procedures.[6b,7,12b]

2-Methylcyclohexan-1,3-dione (2)

To a 1.15 M solution of NaOEt in EtOH (714 mL, 812 mmol) was added diethyl malonate (289.9 g, 1869 mmol) at 0 °C. The cooling bath was removed after addition, and the mixture was stirred for 2 h at r.t. The mixture was then cooled again to –15 °C, and a solution of 1-chloropentan-3-one (**5**; 84.0 g, 696.5 mmol) in abs EtOH (280 mL) was added dropwise under stirring. After the addition, stirring was continued at r.t. for 20 h. The mixture was then cooled to 0 °C, and a 3.1 M solution of NaOEt in EtOH (987 mL, 2219 mmol) was added, and stirring was continued for 72 h. The mixture was then evaporated under vacuum, and a solution of NaOH (616 g, 15.4 mol) in EtOH–H_2O (1:1, 1400 mL) was added to the resulting yellow paste. The mixture was refluxed for 1.5 h, evaporated, acidified to pH 1 with concd HCl (1470 mL), and refluxed for 30 min. After cooling, the solids were filtered and rinsed exhaustively with H_2O to give **2** as a crystalline off-white solid; yield: 62.4 g (71%).

^1H NMR (200 MHz, DMSO-d_6): $\delta = 10.31$ (br s, 1 H), 2.29 (t, $J = 6.2$ Hz, 4 H), 1.80 (quint, $J = 6.2$ Hz, 2 H), 1.53 (s, 3 H).

^{13}C NMR (50 MHz, DMSO-d_6): $\delta = 109.6, 32.5, 20.5, 7.2$.

(–)-(4a*R*)-1,4a-Dimethyl-4,4a,7,8-tetrahydronaphthalene-2,5(3*H*,6*H*)-dione (1)

To triketone **3** (216.0 g, 1028 mmol) dissolved in AcOH (2025 mL) was added D-phenylalanine (169.8 g, previously ground on a mortar) in portions. The mixture was warmed at gentle reflux for 2 h. The reaction flask was cooled to r.t. and AcOH was removed under reduced pressure. The resulting gummy material was suspended in CH_2Cl_2 (2000 mL), whereupon the amino acid precipitated and was removed by filtration. The organic filtrate was washed successively with dilute aq $NaHCO_3$ (2 × 600 mL) and brine (600 mL), and dried ($MgSO_4$). CH_2Cl_2 was removed under reduced pressure giving a brown/orange viscous liquid (158 g). For reasonable batches (20–25 g) standard purifications were performed by chromatography: elution with EtOAc–cyclohexane (1:9) on silica gel. For bigger batches (our case), filtration through a short pad of silica gel usually gave satisfactory results. However, in some cases it was necessary to furtherpurify the yellow oil by high vacuum distillation (bp 115–125 °C/0.2 mmHg). The resulting pale yellow liquid possessed the following optical rotation: $[\alpha]_D^{20}$ –115 ($c = 1.0$, CH_2Cl_2), which meant an optical purity of 82% corresponding to enantiomeric excess measured by ^1H NMR spectroscopy in the presence of $Eu(tfc)_3$. The enantiomeric purification was performed as follows: the crude material was dissolved in Et_2O (560 mL) (sometimes it was necessary to filter through a fluted paper in order to remove small particles). The ethereal solution was cooled to 0–4 °C and seeded with few enantiomerically pure (ee >99%) crystals of (–)-**1** (previously prepared; see, Scheme 5). The solution was left overnight at –15 °C. The resulting crystals were filtered and rinsed with a cold (0 °C) mixture (1:1) of Et_2O–pentane (2 × 200 mL). The crystals (127.2 g)

were dried under high vacuum at r.t.; $[\alpha]_D^{20}$ –140 (c = 1.0, CH_2Cl_2) {Lit.[2] $[\alpha]_D^{20}$ –140 (c = 1.0 in CH_2Cl_2)}. The spectroscopic and physical data were identical to those reported in the literature.[2]

(–)-(*R*)-5,5-(Ethylenedioxy)-1,4a-dimethyl-4,4a,5,6,7,8-hexahydro-2(3*H*)-naphthalenone (9)

Raney Ni (11.35 g wet, 50% in H_2O) was rinsed successively with distilled H_2O (2 × 50 mL) and MeOH (3 × 50 mL) and acetone (3 × 50 mL). The activated Raney Ni was added to acetone (60 mL) under argon. The mixture was refluxed for 30 min. A solution of **8** (600 mg, 1.743 mmol) dissolved in acetone (5 mL) was then added to the warm acetone solution. The refluxing was continued for 6 h. After cooling down, the catalyst was removed by filtration on Celite. The filter cake was rinsed with acetone (3 × 40 mL). Acetone was removed under reduced pressure leaving a yellow oil, which was purified by flash chromatography [silica gel, hexanes–EtOAc (3:1); R_f = 0.3]; yield: 371 mg (90%); very pale yellow oil; $[\alpha]_D^{20}$ –110 (c = 0.5, MeOH) {Lit.[15] $[\alpha]_D^{20}$ –109 (c = 0.53, MeOH)}.

The spectroscopic and physical data were identical to those reported in the literature.[14,15]

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