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TETRAHEDRON: *ASYMMETRY*

First stereoselective synthesis of (4a*S*,5*R*)-4,4a,5,6,7,8-hexahydro-4a,5-dimethyl-2(3*H*)-naphthalenone

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Abstract

The synthesis of enantiomerically pure (4a*S*,5*R*)-hexahydro-4a,5-dimethyl-2(3*H*)-naphthalenone (−)-**1** is described for the first time. The synthesis starts from (*R*)-3-methylcyclohexanone and involves the preparation of Piers enol lactone **6** in its enantiopure form as the key intermediate. Treatment of (+)-**6** with methyl lithium followed by an intramolecular aldol reaction gives the bicyclic enone (−)-**1**.

1. Introduction

As part of our current research program directed to the synthesis of biologically interesting terpene derivatives, we required an efficient method for the preparation of (4a*S*,5*R*)-hexahydro-4a,5-dimethyl-2(3*H*)-naphthalenone (−)-**1**. Several methods have been used to prepare 4,4a,5,6,7,8-hexahydro-4a,5-dimethyl-2(3*H*)-naphthalenone (*rac*-**1**),[1–8] but only two enantioselective routes that give the enantiomer (4a*R*,5*S*)-(+)-**1** have been reported recently[9,10] (Scheme 1). In the first approach, Paquette et al.[9] take advantage of the Wieland–Mischer ketone[11] as a chiral intermediate and introduce the methyl group at C-5 in a six-step sequence. In the second approach, Jenniskens and deGroot[10] use a bicyclic system, prepared from carvone,[12] in which the isopropenyl group must be removed. Although compound (−)-**1** could also be prepared under identical conditions, using (−)-Wieland–Mischer ketone or (−)-carvone as chiral starting materials,[13] we wanted to find a more practical and economic route.

In this paper we describe a short and cheap synthesis for (−)-**1**, which does not require chromatographic purification in any step. The interest of bicyclic enone (−)-**1** lies in its potential as a chiral building block for the enantioselective synthesis of terpenes with the same absolute configuration, such as nominine[14] and aspernomine[15] as well as others of so far unknown absolute configuration, but with the same relative *cis* relationship between the methyl groups, such as nakamurol-A[16] or related compounds with the thelepogane skeleton.[17]

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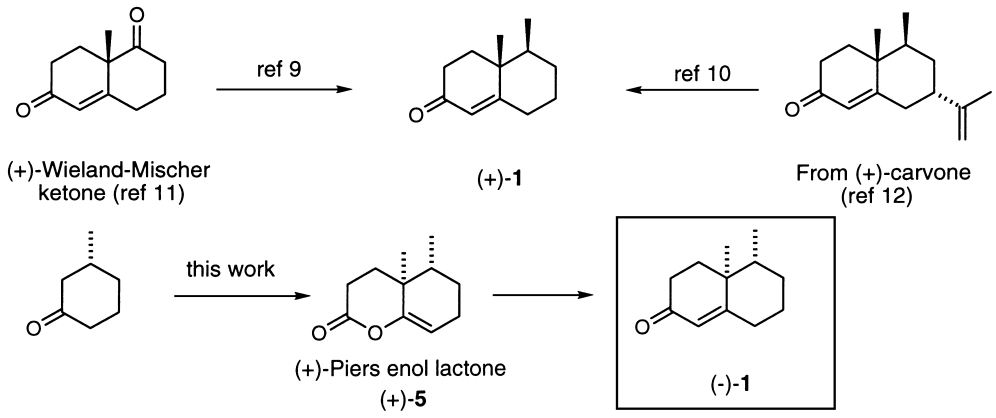
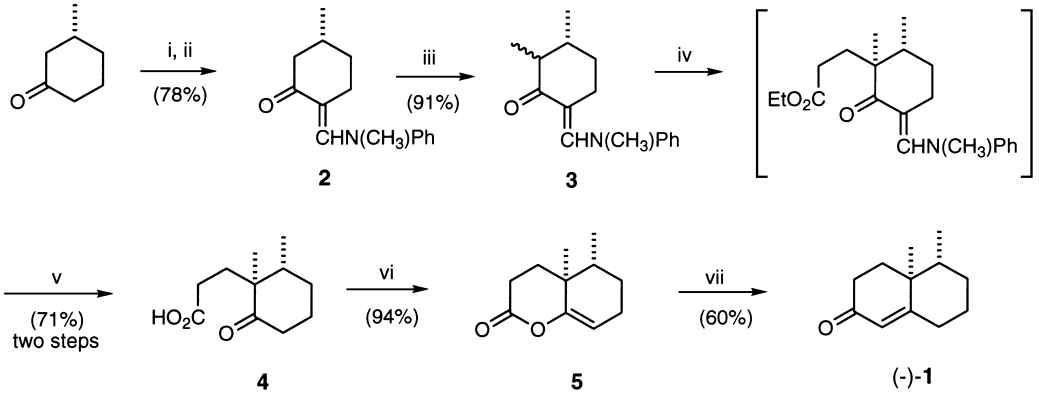


Scheme 1.

2. Results and discussion

The synthesis is outlined in Scheme 2 and takes advantage of Piers' results reported for the racemic series,[2a] described 30 years ago but not exploited in the terpene field. The use of the Piers enol lactone **5** as precursor of **1** allows excellent purification of the *cis*-diastereoisomer, removing by crystallization the minor quantities of the *trans*-epimer that in other approaches to **1** proves remarkably troublesome.



Scheme 2. Reagents and conditions: (i) NaOMe, ethyl formate, MeOH; (ii) *N*-methylaniline, reflux; (iii) LDA, MeI; (iv) *tert*-BuOK, ethyl 3-bromopropionate, *tert*-BuOH; (v) 10% HCl, reflux; then 10% NaOH, reflux; (vi) AcONa, Ac_2O; (vii) MeLi, Et_2O; then KOH, MeOH, reflux. Compound **3** is a 2.5:1 mixture of *trans*- and *cis*-epimers, respectively. For the formation of **4**, the diastereoselection is 7:1. Compound **5**, available in enantiopure form, is formed together with its epimer at C-4a (7:1 ratio) in 94% combined yield

Starting from the commercially available (*R*)-3-methylcyclohexanone, the α-*N*-methylanilinomethylene derivative **2**[18] was obtained in 78% overall yield by formylation at C-6 and subsequent treatment with *N*-methylaniline. Regioselective formation of **2** can be accounted for considering that the initial formylation takes place under thermodynamic control and is governed by the 1,3-allylic strain in the enolate formation step. Treatment of **2** with LDA and methyl iodide furnished the intermediate **3**,[19–21] which was a diastereomeric mixture in a 2.5:1 ratio, the diequatorial isomer (2*S*,3*R*) being the major one. Ketone **3** was alkylated with ethyl bromopropionate to give the corresponding α,α-disubstituted ketone, which, without further purification, was converted to **4**.[22] The result of the alkylation process means that the preferred approach of the electrophilic reagent is from the opposite side of the enolate anion to where the methyl group is placed. However, it cannot be ruled out that the reaction occurs via an

E1cB elimination and Michael addition under thermodynamic control.[23] Keto acid **4** was a 7:1 *cis*:*trans* diastereoisomeric mixture, which could be separated after its transformation into the corresponding enol lactone **5**. Purification of the diastereoisomeric *cis*- and *trans*-**5** was achieved by crystallization, the *cis*-isomer being easily separated using hexane as solvent. Treatment of enantiopure **5** with methyl lithium followed by intramolecular aldol condensation gave the bicyclic enone (−)-**1**. The yield for this final step is 60%. This is not surprising as methyl lithium is acting as a competitive base and gives back either starting material **5** or the acid **4** (via ketene formation).[23] According to the NMR data, which were assigned unequivocally by 2D NMR experiments (COSY, HSQC[24]), (−)-**1** adopts the conformation depicted in Fig. 1.

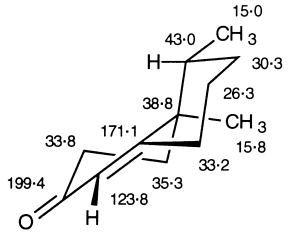


Figure 1. ^{13}C NMR data of **1** (HSQC based assignment)

In conclusion, we have reported an efficient and stereoselective route to the interesting chiral building block (−)-**1**, assembling very efficient classical procedures that allow work on a multigram scale. The seven-step sequence from (*R*)-3-methylcyclohexanone to (−)-**1** includes the blocking of the ketone α-position, two successive alkylations, a deprotecting step, enol lactone formation, and methyl lithium addition followed by aldol cyclization in 25% overall yield. In addition, the entire synthetic procedure to (−)-**1** was performed without any chromatographic separation of diastereomers or other undesired materials.

3. Experimental

3.1. General

^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ solution at 200 MHz, or at 500 MHz when noted, and 50.3 MHz, respectively. In addition, 2D NMR COSY and HSQC experiments were performed on a Varian XL-500 instrument. Chemical shifts are reported as δ values (ppm) relative to internal Me_4Si. Infrared spectra were recorded on a Nicolet 205 FT-IR spectrophotometer. Optical rotations were taken on a Perkin–Elmer Model 241 polarimeter with a 1 ml (*L*=1 dm) cell. TLC was performed on SiO_2 (silica gel 60 F_{254}, Merck). Chromatography refers to flash column chromatography and was carried out on SiO_2 (silica gel 60, SDS, 230–400 mesh). All reactions were carried out under an argon atmosphere with dry, freshly distilled solvents under anhydrous conditions, unless otherwise noted. Drying of organic extracts during the work-up of reactions was performed over anhydrous Na_2SO_4.

3.2. (5R)-5-Methyl-2-(N-methylanilinomethylene)cyclohexanone **2**

To a solution of sodium methoxide, prepared from Na (20 g, 0.88 g-atom) and MeOH, in toluene (500 ml) was added slowly for 30 min a mixture of (3*R*)-3-methylcyclohexanone (50 g, 0.45 mmol) and ethyl formate (71.6 ml, 0.88 mol). The reaction mixture was shaken for 17 h, ice-water was added,

basified with concentrated HCl and extracted with ether. The dried organic extract gave (5*R*)-5-methyl-2-(hydroxymethylene)cyclohexanone (60.5 g), which was used in the next step without purification. ^{1}H NMR 1.02 (d, *J*=6.2 Hz, 3H), 1.12–1.34 (m, 1H), 1.74–1.88 (m, 2H), 1.99 (dd, *J*=18, 10 Hz, 1H), 2.31–2.49 (m, 3H), 8.69 (d, *J*=1.8 Hz, 1H); ^{13}C NMR 21.2 (CH_3), 22.4(CH_2), 27.6 (CH), 30.6 and 39.2 (CH_2), 108.1 (C), 184.1 (C), 187.5 (CH).

A solution of the above hydroxymethylene derivative (60.5 g, 0.43 mol), *N*-methylaniline (49 ml, 0.44 mol) and benzene (750 ml) was heated at reflux in a Dean–Stark apparatus for 13 h. The solvent was removed and the resulting oil was purified by distillation, bp 158–160°C/0.3 mmHg, to give **2**[18] (79 g, 78% for the two steps), which solidified on standing: ^{1}H NMR 0.96 (d, *J*=6.2 Hz, CH_3), 1.05–1.15 (m, 1H), 1.6–2.15 (m, 5H), 2.45 (dm, *J*=15 Hz, 1H), 3.42 (s, NMe), 7.0–7.1 (m, 3H), 7.3 (m, 2H), 7.57 (s, =CH); ^{13}C NMR 21.7 (CH_3), 26.3 (C-4), 29.3 (C-5), 31.6 (C-3), 42.2 (NCH_3), 47.1 (C-6), 110.8 (C-2), 121.1, 123.7, 128.6, 145.7 (Ar), 144.8 (=CH), 198.9 (C-1).

*3.3. (2*RS*,3*R*)-2,3-Dimethyl-6-(*N*-methylanilinomethylene)cyclohexanone **3***

To a solution of LDA (1.6 M in cyclohexane, 30.8 ml, 49.3 mmol) in THF (60 ml) at 0°C was added a solution of ketone **2** (10.76 g, 47 mmol) in THF (100 ml). The solution was stirred for 35 min, methyl iodide (10.3 ml, 164 mmol) was added and the mixture was stirred at room temperature overnight. The reaction mixture was poured into a mixture of aqueous $NaHCO_3$ solution–water–ether. The organic layer was separated and the aqueous phase was extracted with ether. The organic extracts were concentrated to give an oil which was distilled to furnish **3**, as a mixture of diastereomers in a 2.5:1 ratio (10.4 g, 91%): bp 175°C/0.1 mmHg; major isomer (2*S*,3*R*): ^{1}H NMR 1.01 (d, *J*=6.2 Hz, CH_3), 1.20 (d, *J*=7 Hz, CH_3), 3.40 (s, NCH_3), 7.0–7.1 (m, 3H), 7.25–7.35 (m, 2H), 7.54 (t, *J*=1.4 Hz, =CH); ^{13}C NMR 15.5 and 20.8 (CH_3), 26.1 (C-4), 30.9 (C-5), 36.0 (C-3), 42.0 (NCH_3), 49.6 (C-2), 111.3 (C-6), 120.9, 123.7, 128.8 (Ar), 144.7 (=CH), 201.7 (C-1). Minor signals for the isomer 2*R*,3*R* were observed at 12.8 and 16.0 (CH_3), 32.6 and 46.7 (CH), and 202.8 (CO).

*3.4. (1*S*,2*R*)-1,2-Dimethyl-6-oxocyclohexanepropanoic acid **4***

The ketone **3** (20 g, 87 mmol) was added to *tert*-BuOH (200 ml) containing potassium *tert*-butoxide (29.4 g, 0.26 mol) and the resulting solution was stirred at room temperature for 20 min. Ethyl 3-bromopropionate (38.8 ml, 0.30 mol) was added slowly and the mixture was stirred for 1 day. The solvent was removed and the residue was partitioned between ice-water and ether. The aqueous phase was extracted with ether and the combined organic extracts were dried and concentrated to give an oil, which, without purification, was treated with a 10% HCl solution (150 ml) and the mixture was heated at reflux for 30 min. The mixture was cooled and extracted with ether. The organic phase was concentrated and treated with a 10% NaOH solution (150 ml) and the mixture was heated at reflux for 45 min. The mixture was cooled, acidified with 6N HCl solution and extracted with ether. The organic phase was dried and concentrated to give an oil which by distillation gave the carboxylic acid **4** and its epimer in C-1 in a 7:1 ratio (8.2 g, 71%): bp 144–146°C/0.1 mmHg; IR (neat) 2700–3500, 1735, 1705; ^{1}H NMR 0.94 (d, *J*=6.6 Hz, CH_3), 1.04 (s, CH_3), 1.6–1.9 (m, 5H), 1.95–2.1 (m, 2H), 2.2–2.45 (m, 4H), 11.0 (br, 1H, COOH); ^{13}C NMR 15.3 and 18.4 (CH_3), 24.5, 28.9, 29.1, 30.0 and 38.0 (CH_2), 38.4 (CH), 51.2 (C), 179.6 (COOH), 215.4 (CO).

3.5. (4aS,5R)-3,4,4a,5,6,7-Hexahydro-4a,5-dimethyl-2H-1-benzopyran-2-one **5**

A solution of keto acid **4** (14.1 g, 71 mmol) in Ac_2O (320 ml) containing sodium acetate (3 g, 36 mmol) was heated at reflux for 2 h. The solvent was evaporated and the crude was partitioned between water and ether. The organic extracts were washed with aqueous $NaHCO_3$ solution, dried and concentrated. The resulting crude was distilled to give enol lactone **5** (12.1 g, 94%), which corresponds to a 7:1 mixture of *cis*- and *trans*-isomers, respectively. Crystallization with hexane of this mixture gave pure **5**: $[\alpha]_D^{22}$ +153.6 (*c* 1, $CHCl_3$); IR (neat) 1756, 1683; ^{1}H NMR (500 MHz, COSY) 0.91 (d, *J*=6.5 Hz, 3H, 5-CH_3), 1.00 (s, 3H, 4a-CH_3), 1.48 (m, 2H, H-6), 1.6 (m, 2H, H-5 and H-4), 1.85 (dt, *J*=13, 5.2 Hz, H-4_{eq}), 2.06 (m, 2H, H-7), 2.60 (dd, *J*=9.2, 5 Hz, 2H, H-3), 5.26 (t, *J*=4 Hz, 1 H, H-8); ^{13}C NMR (50 MHz, HSQC) 15.0 (5-CH_3), 17.1 (4a-CH_3), 22.8 (C-7), 26.2 (C-6), 27.6 (C-3), 30.6 (C-4), 34.7 (C-4a), 39.0 (C-5), 106.0 (C-8), 154.3 (C-8a), 168.2 (C-2). Anal. calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.05; H, 9.03.

Previous to the crystallization process minor signals corresponding to the C-4a epimer were observed in the ^{13}C NMR spectrum of distilled **5**: 14.6, 20.7, 23.7, 25.8, 26.5, 27.8, 35.0, 37.8, 152.9 and 168.9.

3.6. (4aS,5R)-4,4a,5,6,7,8-Hexahydro-4a,5-dimethyl-2(3H)naphthalenone **1**

To a solution of enol lactone **5** (5.2 g, 29 mmol) in ether (50 ml) cooled to −25°C was quickly added MeLi (1.6 M in ether, 29.1 ml, 46.5 mmol). The resulting solution was stirred at this temperature for 1.5 h and the reaction mixture was poured into 1 N HCl (25 ml) and the product was extracted with ether. To the concentrated organic extract was added a 2.5 N aqueous solution of KOH (30 ml) and MeOH (270 ml) and the mixture was warmed at reflux for 2 h. MeOH was evaporated and the crude was partitioned between water and ether. The organic extracts were concentrated and distilled to give 3 g (60%, 65% based on recovered **4**) of enone (−)-**1**: $[\alpha]_D^{22}$ −183 (*c* 1.63, $CHCl_3$); lit.[9] for (+)-**1**: $[\alpha]_D^{22}$ +185.6 (*c* 1.63, $CHCl_3$); IR (neat) 1675, 1615; ^{1}H NMR (500 MHz, COSY) 0.92 (d, *J*=6 Hz, 5-CH_3), 1.11 (s, 4a-CH_3), 1.45 (m, 3H, H-5, H-6 and H-7), 1.55 (m, 1H, H-6), 1.73 (td, *J*=14, 5 Hz, H-4_{ax}), 1.87 (m, 1H, H-7), 2.03 (ddd, *J*=14, 5, 3.5 Hz, H-4_{eq}), 2.25 (dm, *J*=14.5 Hz, H-8_{eq}), 2.33 (m, 2H, H-8_{ax} and H-3_{eq}), 2.43 (ddd, *J*=16.5, 14, 5, H-3_{ax}), 5.74 (s, H-1); ^{13}C NMR (75 MHz, HSQC) 15.0 (5-CH_3), 15.8 (4a-CH_3), 26.3 (C-7), 30.3 (C-6), 33.2 (C-8), 33.8 (C-3), 35.3 (C-4), 38.8 (C-4a), 43.0 (C-5), 123.8 (C-1), 171.1 (C-8a), 199.4 (C-2).

From the aqueous layer, after acidification and extraction with ether, 500 mg of keto acid **4** was recovered.

Acknowledgements

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