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Efficient Synthesis of the Cyclopentanone Fragrances (Z)-3-(2-oxopropyl)-2-(pent-2-en-1-yl)cyclopentanone and Magnolione

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Abstract

This paper describes the selective syntheses of two *cis*-isomer enriched cyclopentanone fragrances: (Z)-3-(2-oxopropyl)-2-(pent-2-en-1-yl)cyclopentanone (4 steps, 62% overall yield, 67% *cis*) and Magnolione[®] (5 steps, 60% overall yield, 55% *cis*). In addition, the asymmetric synthesis of (3a*R*,7a*S*)-5-methyl-2,3,3a,4,7,7a-hexahydro-1*H*-inden-1-one as well as (3a'*R*,7a'*S*)-5'-methyl-2',3',3a',4',7',7a'-hexahydrospiro[[1,3]dioxolane-2,1'-indene]) has been realized by an efficient kinetic resolution, which enables the selective synthesis of the 2*S*,3*R*-isomer-enriched **3** and **4**.

Keywords

cyclopentanone fragrances; jasmonoids; magnolione; *cis*-selective synthesis; kinetic resolution

1. Introduction

Methyl jasmonate (**1**), the natural fragrant component isolated from *Jasminum grandiflorum* and the blossoms of many other flowers, is widely used in the perfume industry because of its signature jasmine like fragrance.¹ In addition to being an expensive flavor ingredient, **1** has also been identified as a plant hormone that regulates diverse developmental processes (such as seed germination, root growth, fertility, fruit ripening, and senescence) and defense responses (activating plant defense mechanisms in response to insect-driven wounding, various pathogens, and environmental stresses).² Moreover, the anticancer activity of **1** was also reported.³ Methyl dihydrojasmonate (**2**) is a naturally occurring analogue of **1**, which also possesses remarkable olfactory properties. The odor of **2** was described as “sweet, fruity, floral, citrus lemon, and grapefruit-like with woody jasmine and green nuances”. Since the 1970s, racemic mixtures of **2** (*cis:trans* ca. 10:90) have been commercially available (trade name: Hedione[®], by *Firmenich*). Currently, **2** is a highly prized fragrance

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ingredient for the manufacture of high grade perfumes and also finds utility in fruit flavors, tea, tobacco, and laundry products.^{1,4}

The substance (Z)-3-(2-oxopropyl)-2-(pent-2-en-1-yl)cyclopentanone (**3**)⁵ and Magnolione (**4**) are synthetic analogues of **1** and **2** respectively. The odor of **3** and **4** were also found to be characteristic of jasmine. In particular, compared to methyl dihydrojasmonate (**2**), compound **4** is less biodegradable and exhibits a greater odor strength, and a more floral, intense jasminic note.⁶ Magnolione has been commercialized by *Givaudan*,¹ and is used as a precious ingredient in several perfumes (such as 'Coriandre' (*Couturier*, 1973; 13%), 'Eden' (*Cacharel*, 1994; 0.7%)) and thus has attracted considerable attention from the synthetic community.⁷

From a structural point of view, substances **1–4** and many other jasmonoids all possess a 2,3-disubstituted (cyclopentanone numbering) cyclopentanone ring structure. Owing to the two stereogenic centers, four stereoisomers exist, in which the *cis*-isomers are well-known to be unstable and readily epimerize to the corresponding *trans*-diastereomers under thermal, mild Lewis-acidic or basic conditions. It is interesting to note that for **1**, **2** and **4**, only the 2*S*,3*R*-isomers are found to possess very intense, true floral fragrance.¹ For example, 2*S*,3*R*-**4** exhibits the most intense floral, jasmine-like odor of Magnolione, with a threshold concentration of 0.29 ng/L, while the other isomers of **4** only display a very weak jasmine note.^{7d} In this regard, selective syntheses of Magnolione and other jasmonoids with enriched 2*S*,3*R*-isomer content is a highly desirable endeavor of interest for the fragrance industry.

We recently reported total syntheses of several fawcettimine class alkaloids, including Fawcettimine, Fawcettidine, Lycoflexine, and Lycoposerramine B.⁸ We reported that ketal **7**, the Diels-Alder adduct of commercially available isoprene (**5**) and cyclopentenone ethylene ketal (**6**), could be cleaved under Yang's conditions⁹ to afford keto-aldehyde **8** in high yield (Scheme 1). Since **8** contains a masked cyclopentanone moiety with the two *cis*-substituted side chains differentiated at C-2 and C-3, it appeared suitable for the synthesis of *cis*-jasmonoids. Moreover, we have also described the asymmetric synthesis of enantiomerically pure (+)-**7**, our strategy is applicable to the enantioselective synthesis of 2*S*, 3*R*-isomer-enriched cyclopentanone fragrances, which remains a challenging task.^{7c} We have extended this strategy to the synthesis of fragrance components **3** and **4** with high *cis*-isomer content, and report these results herein.

2. Results and discussion

2.1. Racemic syntheses of (Z)-3-(2-oxopropyl)-2-(pent-2-en-1-yl)cyclopentanone and Magnolione

Our syntheses of racemic **3** and **4** from the same intermediate **8** are shown in Scheme 2. Keto-aldehyde **8**, when treated with triphenyl(propylidene)phosphorane, which was generated in situ from *n*-propyltriphenylphosphonium bromide and NaHMDS under reported conditions,^{5b} gave the desired *Z*-alkene **9** in 85% yield, together with some recovered starting material (94% of **9** based on recovered **8**). From **9**, de-ketalization with FeCl₃·SiO₂¹⁰ in acetone provided (Z)-3-(2-oxopropyl)-2-(pent-2-en-1-yl)cyclopentanone (**3**)

(67% *cis*). On the other hand, catalytic hydrogenation of **9** followed by FeCl₃·SiO₂ mediated de-ketalization afforded Magnolione (**4**) (55%, *cis*). The jasmonoids **3** and **4** thus obtained displayed intense jasmine-like odor. It is worthy of note that the stereogenic centers at C-2 of **3** and **4** were partially epimerized under the very mild Lewis acidic conditions, which is in agreement with the observations made by the other groups that the *cis*-isomer readily epimerizes to the *trans*-isomer under thermal, mild Lewis-acidic or basic conditions.¹

2.2. Asymmetric synthesis of (+)-**10** via Diels-Alder reaction

In our syntheses of the fawcettimine class alkaloids, we reported the first asymmetric synthesis of ketal (+)-**7** as well as the corresponding cyclopentanone (+)-**10**. Below, we disclose additional details concerning the syntheses of these two compounds.

Despite the recent progress of chiral Lewis acid-or base-catalyzed asymmetric Diels-Alder (D-A) reactions, the asymmetric reaction involving 2-cyclopenten-1-one (**11**) as the dienophile has only scarcely been recorded.¹¹ In particular, no asymmetric reaction between isoprene (**5**) and **11** was hitherto reported, despite the fact that both **5** and **11** are readily available and widely used in D-A reactions.¹¹

Encouraged by a closely related example reported by Ryu and Corey, wherein 2,3-dimethylbutadiene was allowed to react with **11** in the presence of a chiral, non-racemic oxazaborolidine catalyst provided the D-A adduct in 99% yield and 88:12 e.r., we applied these conditions to the reaction between isoprene (**5**) and 2-cyclopenten-1-one (**11**).^{11c} Pleasingly, when **5** and **11** were treated with (*S*)-(-)-*o*-Tolyl-CBS-oxazaborolidine (**A**) in the presence of Tf₂NH as an activator in toluene at -25 °C for 3 days, adduct (+)-**10** could be isolated in 52% yield with 87:13 e.r. (entry 1, Table 1). The temperature around -25 °C was found to be optimal, since no reaction took place at -42 °C, and the enantioselectivity was diminished at room temperature (Table 1, entries 2 and 3). Running the reaction in CH₂Cl₂ brought no improvement in yield or e.r. of the product (entries 4–6). Other activators such as AlBr₃, TMSOTf, and TFOH were also examined. However, they were found to be less effective than Tf₂NH, with respect to both enantioselectivity and yield (entries 7–13). Finally, oxazaborolidine **B** in the presence of Tf₂NH as activator was tested, giving similar results for (+)-**10** (entry 14).

2.3. Asymmetric synthesis of (+)-**7** and (+)-**10** via kinetic resolution

Since only moderate enantioselectivities of (+)-**10** were obtained via the oxazaborolidine catalyzed D-A reactions, efforts were then focused on the asymmetric synthesis of ketal (+)-**7**. We examined the use of camphorsulfonic acid (CSA) and chiral phosphoric acids in the ionic D-A reaction (Scheme 1, *vide supra*) as well as utilization of chiral auxiliaries, all of which failed to give satisfactory results (no asymmetric induction or inseparable diastereomers).¹² We then found that an efficient kinetic resolution of (±)-**7** could be achieved by Sharpless asymmetric dihydroxylation (Sharpless AD)¹³. Thus when (±)-**7** (67 mg scale) was subjected to the standard Sharpless AD conditions (AD-mix-β, MeSO₂NH₂, K₂CO₃, *t*-BuOH/H₂O (v/v 1:1), 0–4 °C), a steady increase in enantioselectivity for (+)-**7** was observed along with reaction time (Table 2). At 13 hours, (+)-**7** was isolated in 33% yield and greater than 99:1 e.r.

More satisfyingly, when this kinetic resolution was performed on gram quantities of ($\pm$)-**7** (1.94 g), (+)-**7** was isolated in 33% yield with greater than 99:1 e.r. at 7 hours (*s*-factor¹⁴ = 19.3, Scheme 3). With (+)-**7** in hand, the enantioselective syntheses of 2*S*/2*R*, 3*R*-isomers of **3** and **4** in favor of the 2*S*,3*R*-isomer can be readily achieved.

From (+)-**7**, removal of the ketal group of (+)-**7** under acidic conditions afforded cyclopentanone (+)-**10** (Scheme 4).

3. Conclusion

In conclusion, the concise, efficient, and selective syntheses of *cis*-isomer-enriched cyclopentanone fragrances: (*Z*)-3-(2-oxopropyl)-2-(pent-2-en-1-yl)cyclopentanone (**3**) (four steps, 62% overall yield, 67% *cis*) and Magnolione (**4**) (five steps, 60% overall yield, 55% *cis*) have been achieved from commercially available materials. In addition, the asymmetric syntheses of hexahydroindenone (+)-**10** and hexahydroindenone ketal (+)-**7** were realized, which relied on an efficient kinetic resolution via Sharpless asymmetric dihydroxylation technology. These protocols provide a practical, cost-effective approach to the synthesis of 2*S*, 3*R*-isomer enriched **3** and **4**, and may be suited to additional applications in other jasmonoid synthesis as well as in the perfume and cosmetics industry.

4. Experimental section

4.1. General

All reactions were performed in single-neck round bottom flasks fitted with rubber septa under positive pressure of argon with magnetic stirring, unless otherwise noted. Anhydrous solvents were dried by passage through columns of activated alumina. All the reagents were prepared by known literature procedures or used as obtained from commercial sources without further purification, unless otherwise indicated. Reaction progress was monitored by thin-layer chromatography (TLC) carried out on 0.25 mm coated commercial silica gel plates impregnated with a fluorescent indicator (254 nm) visualized by UV light and/or submersion in standard TLC stains (KMnO₄, Vanillin, Anisaldehyde, etc.) followed by heating on a hot plate (~200 °C, 15 s). Flash column chromatography was performed on silica gel (230–400 mesh), unless otherwise indicated. ¹H and ¹³C NMR spectra were obtained from 300 MHz or 400 MHz spectrometers. The chemical shifts are given in parts per million (ppm) relative to TMS at δ 0.00 ppm or to residual CDCl₃ δ 7.27 ppm for proton spectra and relative to CDCl₃ at δ 77.23 ppm for carbon spectra, unless otherwise noted. IR spectra were recorded on a Perkin-Elmer 1600 FTIR spectrophotometer using NaCl plates. High-resolution mass spectra were obtained by a Fisons VG Autospec spectrometer using simultaneous electrospray ionization (ESI). Enantiomeric ratios (e.r.) were measured on a GC or HPLC device using a chiral column. Optical rotations were recorded on a polarimeter at a wavelength of 589 nm. Unless otherwise noted, all compounds are racemates although they are indicated as a single enantiomer.

4.2. Procedures and characterization of new compounds

Note: Procedures and data for ($\pm$)-**7**, (+)-**7**, **8**, (+)-**10**, (–)-**12** have been reported in Ref. 8 and will not be reiterated below.

4.2.1. 1-((6S,7R)-6-((Z)-pent-2-en-1-yl)-1,4-dioxaspiro[4.4]nonan-7-yl)propan-2-one (9)—To a stirred solution of Ph_3PPrBr (0.2643 g, 0.64 mmol, 1.1 equiv.) in THF (5 mL) at room temperature was added NaHMDS (1.0 M in THF, 0.64 mL, 0.64 mmol, 1.1 equiv.). After stirring at room temperature for 5 minutes, the flask was cooled to $-42\text{ }^\circ\text{C}$ (dry ice/ CH_3CN bath). Keto-aldehyde **8** (0.1315 g, 0.58 mmol, 1.0 equiv.) in THF (5 mL) was added in one portion. After 30 minutes at $-42\text{ }^\circ\text{C}$, the reaction was allowed to warm to room temperature and filtered over a short pad of silica, washed with EtOAc (15 mL). The filtrate was concentrated and the residue was purified by flash chromatograph (Hexanes/EtOAc 6:1) to give recovered **8** (0.0127 g, 10%) and title compound (0.1244 g, 85%) as a colorless oil.

$R_f = 0.33$, Hexanes/EtOAc 6:1; IR (thin film): 2963, 2878, 1716, 1437, 1356, 1154, 1038 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ 5.22–5.37 (m, 2H), 3.78–3.91 (m, 4H), 2.52–2.60 (m, 1H), 2.36–2.50 (m, 2H), 1.91–2.14 (m, 8H), 1.70–1.87 (m, 3H), 1.28–1.36 (m, 1H), 0.93 (t, $J = 7.6\text{ Hz}$, 3H); ^{13}C NMR (75 MHz, CDCl_3): δ 208.9, 132.1, 127.9, 117.8, 65.0, 64.3, 49.0, 44.3, 34.9, 34.6, 30.4, 27.4, 22.3, 20.9, 14.3; HRMS (ESI) calcd. for $\text{C}_{15}\text{H}_{25}\text{O}_3$ $[\text{M}+\text{H}]^+$ 253.1798 found 253.1803.

4.2.2. (Z)-3-(2-oxopropyl)-2-(pent-2-en-1-yl)cyclopentanone (3)—To a solution of ketal **9** (0.0323 g, 128 μmol , 1.0 equiv.) in acetone (ACS grade, 2 mL) was added $\text{FeCl}_3\cdot\text{SiO}_2^{10}$ (0.014 g). After stirring at room temperature for 5 h, the mixture was filtered over a short pad of silica gel, and washed with EtOAc (5 mL). The filtrate was concentrated under reduced pressure and the residue was purified by flash chromatography (hexanes/EtOAc 7:1) to give title compound (0.0245 g, 92%, 67% *cis*) as a colorless oil.

$R_f = 0.19$, hexanes/EtOAc 6:1; IR (thin film): 2963, 1738, 1716, 1459, 1408, 1357, 1263 cm^{-1} ; ^1H NMR (400 MHz, *cis* and *trans*, CDCl_3): δ 5.39–5.47 (m, 1H), 5.22–5.31 (m, 1H), 2.79–2.90 (m, 1H), 2.42–2.55 (m, 1H), 2.18–2.40 (m, 5H), 2.16 (s, 1H), 2.15 (s, 2H), 1.96–2.08 (m, 3H), 1.23–1.86 (m, 2H), 0.92–0.98 (m, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ *cis* isomer: 219.5, 207.5, 133.5, 125.9, 52.5, 43.0, 35.6, 34.5, 30.5, 26.0, 23.4, 20.9, 14.3; *trans* isomer: 219.3, 207.5, 134.2, 125.4, 54.2, 48.6, 38.0, 37.2, 30.7, 27.6, 25.8, 20.8, 14.3; HRMS (ESI) calcd. for $\text{C}_{13}\text{H}_{21}\text{O}_2$ $[\text{M}+\text{H}]^+$ 209.1536 found 209.1532.

4.2.3. Magnolione®(4)—To a solution of ketal **9** (0.0296 g, 116 μmol , 1.0 equiv.) in EtOAc (ACS grade, 2 mL) was added Pd/C (0.0015 g, 5 Wt.%). The mixture was stirred under 1 atm of H_2 at room temperature for 24 h. The mixture was then filtered and concentrated under reduced pressure. The residue was dissolved in acetone (ACS grade, 2 mL). $\text{FeCl}_3\cdot\text{SiO}_2$ (0.005 g) was added and the mixture was stirred at room temperature. After 7 hours, the mixture was filtered and concentrated at reduced pressure. The residue was purified by flash chromatography (hexanes/EtOAc 7:1) to give title compound (0.0243 g, 90% over 2 steps, 55% *cis*) as a colorless oil.

$R_f = 0.15$, hexanes/EtOAc 7:1; IR (thin film): 2956, 2931, 2860, 1738, 1717, 1462, 1409, 1357, 1237, 1163, 1101 cm^{-1} ; ^1H NMR (400 MHz, *cis* and *trans*, CDCl_3): δ 2.72–2.89 (m, 1H), 2.42–2.50 (m, 1H), 1.96–2.39 (m, 7H), 1.10–1.76 (m, 10H), 0.85–0.91 (m, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ *cis* isomer: 219.8, 207.6, 52.6, 42.9, 35.4, 34.6, 32.1, 30.6, 27.4,

25.9, 25.0, 22.7, 14.3; *trans* isomer: 220.1, 207.7, 54.4, 48.7, 38.0, 37.2, 32.3, 30.7, 28.1, 27.6, 26.6, 22.7, 14.3; HRMS (ESI) calcd. for C₁₅H₂₃O₂ [M+H]⁺ 211.1693 found 211.1695.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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15. The stereochemistry for the two hydroxyl groups on compound **12** was not determined.

Methyl jasmonate (1)

Methyl dihydrojasmonate (2)

(Z)-3-(2-oxopropyl)-2-(pent-2-en-1-yl)cyclopentanone (3)

Magnolione[®] (4)

Figure 1.
Structures of some jasmonoid fragrances.

Scheme 1.
Synthesis of keto-aldehyde **8**.

Scheme 2.
Syntheses of **3** and **4**.

Scheme 3. Sharpless asymmetric dihydroxylation of $(\pm)\text{-7}$ (1.94 g scale).

Scheme 4.
Synthesis of (+)-**10** from (+)-**7**.

Table 1

Catalytic asymmetric synthesis of (+)-**10** by Corey catalysts.^a

Entry	Catalyst (mol%)	Solvent	Time	T (°C)	e ^b (%)	Y ^c (%)
1	A /Ti ₂ NH (20)	PhMe	3d	-25	87:13	52
2	A /Ti ₂ NH (20)	PhMe	1d	-42	—	n.r.
3	A /Ti ₂ NH (20)	PhMe	40h	r.t.	75:25	15
4	A /Ti ₂ NH (20)	CH ₂ Cl ₂	3d	-20	86:14	56
5	A /Ti ₂ NH (20)	CH ₂ Cl ₂	10d	-30	88.5:11.5	38
6	A /Ti ₂ NH (10)	CH ₂ Cl ₂	4d	-20	69:31	40
7	A /AlBr ₃ (5)	PhMe	3d	-20	85.5:14.5	14
8	A /AlBr ₃ (5)	CH ₂ Cl ₂	4d	-30	82.5:17.5	5
9	A /AlBr ₃ (5)	PhMe/CH ₂ Cl ₂	30h	-42	91:9	7
10	A /AlBr ₃ (5)	PhMe/Et ₂ O	4d	-20	82:18	21
11	A /AlBr ₃ (5)	PhMe/CH ₃ CN	4d	-20	87.5:12.5	9
12	A /TMSOTf (10)	PhMe	1d	-78	83:17	24
13	A /TfOH (20)	PhMe	1d	-30	87:13	<5
14	B /Ti ₂ NH (20)	CH ₂ Cl ₂	7d	-20	87:13	60

^aReactions were performed on 0.4 mmol scale of **11**.^bDetermined by GC using chiral column.^cIsolated yield.

Table 2Sharpless asymmetric dihydroxylation on ($\pm$)-**7** (67 mg scale).^a

Entry	Time (h)	e.r. of (+)- 7 ^b
1	1	<<70:30
2	2	<70:30
3	3	71:29
4	4	78.5:21.5
5	5	88:12
6	6	94.5:5.5
7	7	98.5:1.5
8	8	99:1
9 ^c	13	> 99.5:0.5

^aReaction was performed on 67 mg of ($\pm$)-**7**.^bDetermined by GC using chiral column.^c33% of (+)-**7** and 60% of (–)-**12**¹⁵ were isolated.