Straightforward Synthesis of (*R*)-(−)-Kjellmanianone

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Abstract: A direct route to enantiomerically pure (−)-kjellmanianone is reported. The synthesis involves a cerium-catalyzed α-hydroxylation and an enzyme-catalyzed procedure to resolve tertiary alcohols at key stages. The intermediate β-oxo ester was α-hydroxylated to give good yields of racemic kjellmanianone. The resolution of the racemic material was achieved by enzymatic saponification, followed by a chemical decarboxylation sequence to give enantiopure (−)-kjellmanianone with 99% ee. Bromination then afforded the (−)-bromo derivative, whose X-ray structure provided evidence for the *R* configuration of (−)-kjellmanianone.

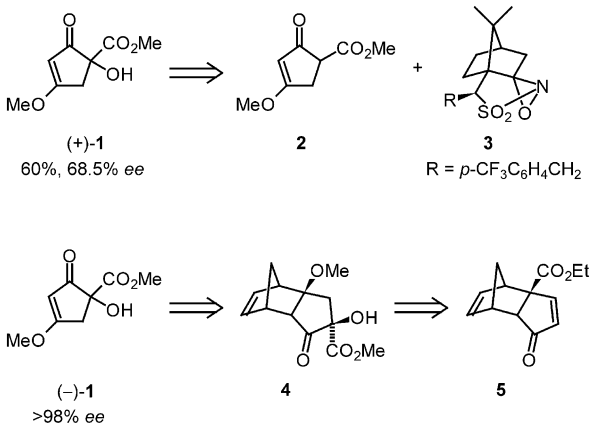
Keywords: cerium catalysis · dicarbonyl compounds · kinetic resolution · lipase · structure elucidation

Introduction

The cyclopentenoid antibiotic (+)-kjellmanianone 1 was isolated from marine algae *Sargassum kjellmanianum* Yendo and was first reported in 1980.[1] The compound exhibits antibacterial activity against gram-positive microorganisms such as *E. coli* K12 and *Bacillus subtilis* var. *niger*. The first enantioselective synthesis realized by Smith[2] and Davis[3] was based on the α-hydroxylation of β-oxo ester **2** with optically active oxaziridine **3** (Davis reagent),[4] giving compound (+)-**1** in 60% yield with 68.5% ee.[5] The authors postulated the absolute configuration of (+)-**1** from CD spectra by the exciton chirality method to be the *R* configuration (Scheme 1).

In 1994 Zwanenburg et al. published a second stereospecific synthetic strategy resulting in (*R*)-**1**.[6] A retro-Diels–Alder reaction[7] of **4** was the key step, resulting in virtually enantiopure **1**. The six-step route started from optically active tricycle **5** (Scheme 1). Interestingly, these authors established the *R* configuration for (−)-**1** based on X-ray diffraction analysis of the precursor **4**, in contrast to Smith and Davis.[6b] Up to now the absolute configuration of kjellmanianone is still discussed controversially.

In this paper we report a simple approach to β-oxo ester **2** followed by its α-hydroxylation with molecular oxygen in a cerium-catalyzed process,[8] to give racemic kjellmanianone 1. This racemate was resolved enzymatically to yield (−)-**1** with 99% ee. After bromination with retention of configuration, the absolute configuration of (−)-**1** was established to be *R*, in accordance with the results of Zwanenburg.



Scheme 1. Literature routes to optically active kjellmanianone. The absolute configuration of both (+)-**1** and (−)-**1** was contradictory reported to be the *R* configuration.

Results and Discussion

Smith and Davis prepared β-oxo ester **2** by methoxycarbonylation of the enol ether derived from 1,3-cyclopentadione, which is commercially available, but expensive. Curiously, the most efficient synthetic approach to 1,3-cyclopentadione occurs via oxo ester **2**.[9] We therefore modified a known procedure to prepare oxo ester **2** from a commercially available bulk material, the chloro derivative of methyl acetoacetate **6**.[10] Nucleophilic substitution of **6** with dimethyl malo-

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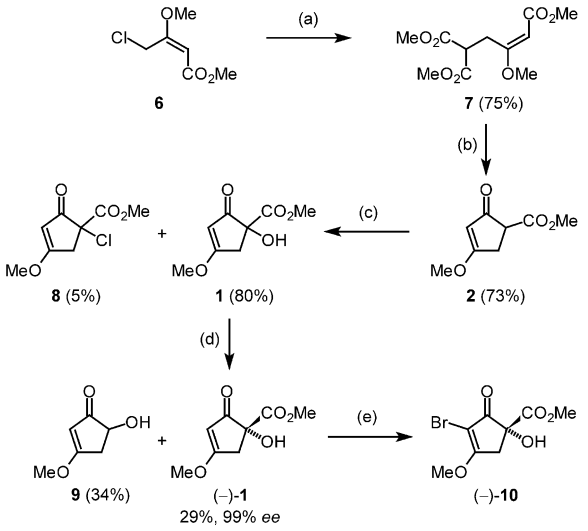
nate in DMF gave intermediate triester **7** (75%), which was subsequently converted to β-oxo ester **2** (73%) by Dieckmann condensation (Scheme 2). Derivative **2** was α-hydroxylated under an atmosphere of oxygen with catalytic amounts of $CeCl_3 \cdot 7H_2O$ to give racemic kjellmanianone 1 in 80% yield. Chloro derivative **8** was obtained as a by-product (5%) separated by column chromatography.



Scheme 2. Four-step reaction to (−)-kjellmanianone 1. a) $CH_2(CO_2Me)_2$, NaOMe, DMF, 23 °C, 48 h; b) NaOMe, MeOH, 65 °C, 3.5 h; c) 5 mol% $CeCl_3 \cdot 7H_2O$, 1 atm O_2, *i*PrOH, 23 °C, 17 h; d) *Candida antarctica* lipase B, toluene/phosphate buffer, 35–40 °C, 48 h; e) Br_2, CCl_4, −4 °C→23 °C, 13 h.

The enzyme-catalyzed transesterification is an established strategy for the resolution of racemic secondary alcohols. However, the application of this method to tertiary alcohols is less common.[11] In order to resolve the racemate **1** we have chosen a sequence of enzymatic saponification followed by chemical decarboxylation, a concept which is so far rarely precedented in the literature.[12] We utilized the readily available lipase B from *Candida antarctica*. CAL B converted the (+)-enantiomer of **1** specifically to yield the α-hydroxyketone **9**. From the reaction mixture kjellmanianone ((−)-**1**) was recovered with 29% yield (58% based on the (−)-enantiomer in the racemate) and 99% ee. After developing GC conditions for baseline resolution on a chiral phase using the racemic material, the optical purity of (−)-**1** was confirmed by GC.

As mentioned in the introduction, contradictory statements are found in the literature concerning the absolute configuration of optically active kjellmanianone. Thus, to establish the stereochemistry of our material, we prepared a series of derivatives containing S, Br, or Si atoms by esterification or etherification of the tertiary alcohol function in **1**. Unfortunately, all efforts failed to obtain single crystalline products in this way. Therefore, we finally treated compound **1** with bromine in CCl_4 to prepare a derivative with bromine functionalization and a maintained hydroxy group at the five-membered ring. In this manner we obtained the racemic and optically active compound **10**. Enantiopure (−)-**10** gave single crystals suitable for X-ray crystallographic analysis enabling the elucidation of the absolute configuration (Figure 1).[13]

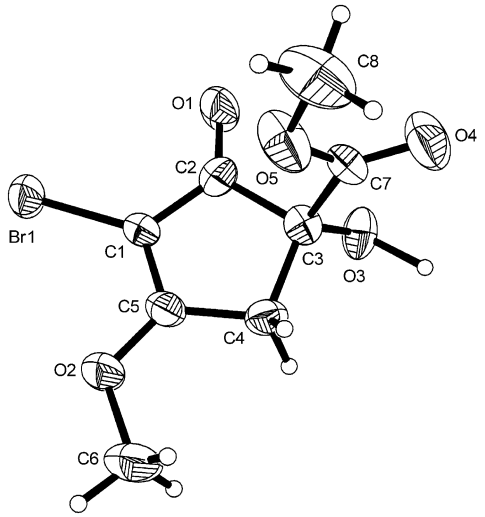


Figure 1. ORTEP view of bromo derivative (−)-**10**, derived from (−)-kjellmanianone ((−)-**1**).

The X-ray crystal structure of enantiomer (−)-**10**, prepared from (−)-**1**, unambiguously confirms the *R* configuration. Since retention of the quaternary stereocenter configuration during bromination/dehydrobromination can be assumed, we conclude (−)-kjellmanianone ((−)-**1**) is also the *R* enantiomer. This finding agrees with the observation of Zwanenburg et al. and contradicts the proposal of Smith and Davis. The optical rotation of $[\alpha]_{20}^{D} = -111$ ($c = 2.3\ g\,dm^{-3}$ in $CHCl_3$) for the enantiopure compound (−)-**1** (99% ee) also corresponds with the literature data $[\alpha]_{20}^{D} = -115$ ($c = 1.15\ g\,dm^{-3}$ in $CHCl_3$).[6]

Conclusion

In a straightforward three-step synthesis racemic kjellmanianone 1 is accessible from precursor allyl chloride **6** via β-oxo ester **2** as the key intermediate. The hydroxylation of **2** with molecular O_2 as an oxidant and the cerium catalyst $CeCl_3 \cdot 7H_2O$ is an environmentally benign alternative to other reagents, such as peracids or oxaziridines utilized in stoichiometric amounts. With a novel concept for enzymatic resolution of α-hydroxy-β-oxo esters by lipase-mediated saponification and decarboxylation we isolated enantiopure (−)-kjellmanianone 1. After functionalization of (−)-**1** with bromine to yield the corresponding bromo derivative (−)-**10**, the absolute configuration of the latter could unequivocally be determined by X-ray crystallography to be the *R* configuration. As bromination is assumed to proceed with retention of configuration, we concluded that (−)-kjellmanianone ((−)-**1**) is also the *R* enantiomer.

Experimental Section

General methods: Chloride **6** and *Candida antarctica* lipase B are commercially available. Column chromatography was carried out using Merck SiO_2 60 with hexanes (PE, b.p. 40–60 °C) and ethyl acetate (EA) as eluents. ^{13}C NMR multiplicities were determined with DEPT experiments.

Dimethyl (*E*)-3-methoxy-5-methoxycarbonyl-2-hexenedioate (7): NaOMe (321 mg, 5.94 mmol) was added portionwise at 23 °C to a solution of dimethyl malonate (820 mg, 6.21 mmol) in absolute DMF (3.5 mL). After stirring for 10 min, chloride **6** (420 mg, 2.55 mmol) was added dropwise over 10 min, and the reaction mixture was stirred for 24 h at 23 °C. After addition of further DMF (6.0 mL), dimethyl malonate (400 mg, 3.03 mmol) and NaOMe (176 mg, 3.25 mmol) and stirring for a further 24 h, all volatile materials were removed under vacuum. The residue was taken up in H_2O (20 mL), neutralized with conc. HCl and extracted with CH_2Cl_2 (3×20 mL). The combined extracts were dried ($MgSO_4$) and concentrated. The residue was purified by chromatography on SiO_2 (PE:EA 2:1, R_f=0.28) to give **7** as a colorless oil (494 mg, 1.90 mmol, 75 %). B.p. 140–141 °C/3 mbar; ^1H NMR (500 MHz, $CDCl_3$): δ=3.41 (d, J=7.7 Hz, 2H; CH_2), 3.61 (s, 3H; CH_3), 3.68 (s, 3H; CH_3), 3.73 (s, 6H; CH_3), 3.76 (t, J=7.8 Hz, 1H; CH), 5.08 ppm (s, 1H; CH); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ=31.19 (CH_2), 49.18 (CH_3), 51.00 (CH), 52.61 (CH_3), 55.82 (CH_3), 91.89 (CH), 167.57 (C=O), 169.14 (C), 171.62 ppm (C=O); IR (KBr): $\tilde{\nu}$3015 (w), 2953 (w), 2846 (w), 1748 (s), 1705 (s), 1628 (s), 1438 (m), 1382 (m), 1342 (w), 1290 (m), 1235 (m), 1196 (m), 1141 (s), 1047 (m), 929 (m), 828 (m), 748 cm^{-1} (w); MS (CI, CH_4): m/z (%): 261 (46) [MH$^+$], 243 (12), 229 (100) [M^+-CH_3OH], 196 (25), 169 (28), 141 (24), 125 (5), 69 (2), 59 (3); elemental analysis: calcd (%) for $C_{11}H_{16}O_7$ (260.24): C 50.77, H 6.20; found: C 50.33, H 6.22.

Methyl 1-methoxy-3-oxocyclopentene-4-carboxylate (2): Under N_2 atmosphere with exclusion of moisture and air, sodium (1.100 g, 47.85 mmol) was added portionwise to absolute methanol (10 mL) and heated at 65 °C for 0.5 h. A solution of **7** (6.000 g, 23.06 mmol) in absolute methanol (10 mL) was added dropwise over 20 min, and the reaction mixture stirred at 65 °C for a further 3.5 h. Then HOAc (3 mL) and H_2O (40 mL) were added, and the reaction mixture extracted with CH_2Cl_2 (4×20 mL). The combined extracts were dried ($MgSO_4$), and after removal of the solvent under vacuum, the residue was purified by chromatography on SiO_2 (PE:EA 1:1, R_f=0.20) to give **2** as a yellow oil (2.851 g, 16.75 mmol, 73 %). ^1H NMR (300 MHz, $CDCl_3$): δ=2.80 (ddd, J=17.7, 7.6, 1.1 Hz, 1H; C*H*H), 3.06 (ddd, J=17.7, 3.1, 1.2 Hz, 1H; CH*H*), 3.55 (dd, J=7.6, 3.1 Hz, 1H; CH), 3.78 (s, 3H; CO_2CH_3), 3.88 (s, 3H; OCH_3), 5.30 ppm (t, J=1.1 Hz, 1H; CH); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ=32.13 (CH_2), 51.73 (CH), 53.12 (CH_3), 59.56 (CH_3), 103.02 (CH), 169.89 (C), 191.18 (C=O), 198.37 ppm (C=O); IR (KBr): $\tilde{\nu}$3125 (w), 3073 (w), 2976 (w), 2924 (w), 2872 (w), 2824 (w), 1766 (s), 1717 (m), 1668 (m), 1623 (m), 1567 (s), 1481 (s), 1404 (m), 1383 (m), 1338 (m), 1194 (s), 1129 (s), 1050 (m), 966 (m), 901 cm^{-1} (m); MS (EI, 70 eV): m/z (%): 170 (100) [M^+], 139 (58) [M^+-OMe], 127 (23), 111 (63) [M^+-CO_2Me], 83 (20), 69 (34), 59 (18); elemental analysis: calcd (%) for $C_8H_{10}O_4$ (170.16): C 56.77, H 5.92; found: C 56.41, H 5.94.

Methyl 1-hydroxy-4-methoxy-2-oxo-3-cyclopentenecarboxylate (1): $CeCl_3 \cdot 7H_2O$ (140 mg, 0.376 mmol) was added to a solution of **2** (1.320 g, 7.757 mmol) in *i*PrOH (2.6 mL). The flask was then evacuated to 300 mbar, flushed with O_2, and the reaction mixture was stirred at 23 °C for 17 h, while a slow stream of oxygen (ca. 50 cm^3h^{-1}) was passed through. After removal of the solvent, the residue was purified by chromatography on SiO_2 [PE:EA 2:1→1:1, R_f(PE/EA 1:1)=0.21] to give **1** as a colorless crystalline solid (1.159 g, 6.226 mmol, 80 %), m.p. 131 °C, and by-product **8** [R_f(PE/EA 1:1)=0.31] as a brown oil (0.081 g, 0.40 mmol, 5 %).

Racemic 1: ^1H NMR (500 MHz, $CDCl_3$): δ=2.75 (d, J=17.7 Hz, 1H; C*H*H), 3.18 (d, J=17.7 Hz, 1H; CH*H*), 3.80 (s, 3H; CO_2CH_3), 3.95 (s, 3H; OCH_3), 3.97 (s, 1H; OH), 5.36 ppm (s, 1H; CH); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ=40.56 (CH_2), 53.45 (CH_3), 59.23 (CH_3), 79.06 (C), 101.08 (CH), 171.53 (C), 190.02 (C=O), 199.50 ppm (C=O); IR (KBr): $\tilde{\nu}$3346 (br s), 3083 (m), 2955 (w), 1746 (s), 1696 (s), 1597 (s), 1453 (m), 1428 (m), 1368 (s), 1272 (m), 1241 (m), 1201 (s), 1170 (s), 1115 (s), 1021 cm^{-1} (w); MS (EI, 70 eV): m/z (%): 186 (82) [M^+], 170 (95) [M^+-CH_4], 139 (18) [M^+-OMe], 127 (79) [M^+-CO_2Me], 111 (100), 98 (78), 69 (58), 59 (26); elemental analysis: calcd (%) for $C_8H_{10}O_5$ (186.16): C 51.61, H 5.41; found: C 51.70, H 5.47. GC: Lipodex E (25 m×0.25 mm, 0.25 μm), 0.5 bar H_2, 20 °K min^{-1} gradient from 40 °C to 80 °C, 3 min at 80 °C, 10 °K min^{-1} gradient from 80 °C to 200 °C, t_R((*S*)-**1**)=18.8 min, t_R((*R*)-**1**)=20.1 min.

By-product 8: ^1H NMR (500 MHz, $CDCl_3$): δ=3.02 (d, J=18.0 Hz, 1H; C*H*H), 3.61 (dd, J=18.2, 1.2 Hz, 1H; CH*H*), 3.84 (s, 3H; CO_2CH_3), 3.95 (s, 3H; OCH_3), 5.38 ppm (s, 1H; CH); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ=44.55 (CH_2), 54.18 (CH_3), 59.54 (CH_3), 66.37 (C), 100.63 (CH), 167.37 (C), 188.28 (C=O), 193.89 ppm (C=O); IR (film): $\tilde{\nu}$2954 (w), 2928 (w), 1762 (m), 1712 (m), 1596 (s), 1448 (w), 1427 (w), 1359 (m), 1290 (w), 1249 (m), 1169 (m), 1029 cm^{-1} (w); MS (EI, 70 eV): m/z (%): 204 (94) [M^+], 172 (76) [M^+-CH_3OH], 169 (90) [M^+-Cl], 161 (56), 145 (46) [$M^+-CO_2CH_3$], 137 (100), 69 (72), 59 (20); elemental analysis: calcd (%) for $C_8H_9ClO_4$ (204.61): C 46.96, H 4.43; found: C 47.50, H 4.63.

Kinetic resolution of racemic 1 using *Candida antarctica* lipase B: The lipase (20 mg) was added to a solution of racemic **1** (209 mg, 1.12 mmol) in toluene (4 mL) and phosphate buffer (100 mM, pH 7, 10 mL), and the reaction mixture was stirred at 35–40 °C for 48 h. During the reaction, the pH was controlled and, if necessary, adjusted to pH 7 with a 1 M NaOH solution. The resolution was followed by taking aliquots of 5 μL, which were directly analyzed by GC on a chiral phase. After extraction with CH_2Cl_2 (4×20 mL), the layers were separated. The organic layer was dried ($MgSO_4$) and concentrated under vacuum to give (−)-**1** as a colorless crystalline solid (61 mg, 0.33 mmol, 29 %); $[\alpha]_{20}^D$=−111 (c=2.3 g dm^{-3} in $CHCl_3$), 99 % ee; GC: Lipodex E (25 m×0.25 mm, 0.25 μm), 0.5 bar H_2, 20 °K min^{-1} gradient from 40 °C to 80 °C, 3 min at 80 °C, 10 °K min^{-1} gradient from 80 °C to 200 °C, t_R((*R*)-**1**)=20.1 min. The aqueous layer was acidified with 1 M HCl and extracted with EA (3×16 mL). The combined extracts were dried ($MgSO_4$) and concentrated under vacuum to give **9** as a yellow oil (48.6 mg, 0.38 mmol, 34 %). ^1H NMR (500 MHz, $CDCl_3$): δ=2.59 (ddd, J=1.1, 3.2, 17.4 Hz, 1H; C*H*H), 2.97 (ddd, J=1.1, 7.1, 17.4 Hz, 1H; CH*H*), 3.49 (s, 1H; OH), 3.89 (s, 3H; OCH_3), 4.32 (dd, J=3.2, 7.0 Hz, 1H; CH), 5.31 ppm (s, 1H; CH); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ=37.11 (CH_2), 58.76 (CH_3), 71.31 (CH), 101.86 (CH), 188.73 (C), 205.60 ppm (C=O); IR (film): $\tilde{\nu}$3380 (br s), 2921 (m), 2852 (w), 1684 (m), 1585 (s), 1447 (w), 1363 (m), 1249 (m), 1200 (m), 1158 (w), 1082 (m), 980 cm^{-1} (m); MS (EI, 70 eV): m/z (%): 128 (16) [M^+], 111 (6) [M^+-OH], 98 (6), 86 (4), 69 (13), 44 (25), 18 (100); HRMS: calcd for $C_6H_8O_3$: 128.0473; found: 128.0473 [M^+].

Methyl *rac*-2-bromo-4-hydroxy-1-methoxy-3-oxocyclopentene-4-carboxylate (10): Compound **1** (52 mg, 0.28 mmol) was added to bromine (70 mg, 0.44 mmol) in CCl_4 (0.4 mL) at −4 °C under inert gas atmosphere. The reaction mixture was allowed to warm up to room temperature (13 h) with stirring. After removal of all volatile materials under vacuum, the crude product was purified by chromatography on SiO_2 (PE:EA 1:1, R_f=0.09) to give **10** as a colorless crystalline solid (18 mg, 0.068 mmol, 24 %). M.p. 179–182 °C; ^1H NMR (500 MHz, $CDCl_3$): δ=2.86 (d, J=17.2 Hz, 1H; C*H*H), 3.36 (d, J=17.3 Hz, 1H; CH*H*), 3.82 (s, 3H; CO_2CH_3), 3.92 (br s, 1H; OH), 4.17 ppm (s, 3H; OCH_3); $^{13}C\{^1H\}$ NMR (63 MHz, $CDCl_3$): δ=38.75 (CH_2), 53.84 (CH_3), 58.58 (CH_3), 77.53 (C), 95.38 (C), 171.57 (C), 183.88 (C=O), 192.92 ppm (C=O); IR (ATR): $\tilde{\nu}$3374 (m, br), 2957 (w), 2921 (w), 2851 (w), 1744 (s), 1696 (s), 1585 (s), 1460 (w), 1429 (m), 1404 (w), 1360 (s), 1302 (m), 1265 (s), 1204 (s), 1178 (s), 1126 (s), 1080 (m), 1058 cm^{-1} (m); MS (EI, 70 eV): m/z (%): 264 (24) [M^+], 246 (100) [M^+-H_2O], 205 (29) [M^+-CO_2Me], 176 (9), 147 (16), 125 (28), 83 (10), 43 (10); HRMS: calcd for $C_8H_9BrO_5$: 263.933; found: 263.933 [M^+]; GC: Bondex unβ, 0.4 bar H_2, 3 min at 100 °C, then 2.5 °K min^{-1} gradient to 200 °C, t_R((*S*)-**10**)=29.5 min, t_R((*R*)-**10**)=30.0 min.

Methyl (*R*)-2-bromo-4-hydroxy-1-methoxy-3-oxocyclopentene-4-carboxylate ((*R*)-(−)-10): Analogous to the procedure described for racemic **10**, optically active (−)-**10** was prepared from (−)-**1** (52 mg, 0.28 mmol). Crystallization from EA and PE gave single crystals suitable for X-ray crystal analysis; $[\alpha]_{20}^D$=−97 (c=0.7 g dm^{-3} in $CHCl_3$); GC: Bondex unβ, 0.4 bar H_2, 3 min at 100 °C, then 2.5 °K min^{-1} gradient to 200 °C, t_R((*R*)-**10**)=30.0 min, ≥99 % ee.

X-ray crystal structure analysis: $C_8H_9BrO_5$, M=265.06, 0.25×0.20×0.20 mm, crystal system, orthorhombic, space group, $P2_12_12_1$, a=7.7476(4), b=7.9475(3), c=16.5420(9) Å, $\alpha=\beta=\gamma=90°$, V=1018.56(9) $Å^3$, ρ_{calcd}=1.729 g cm^{-3}, Z=4, μ=5.516 mm^{-1}, T=293(2) K,

$\lambda = 1.54178$ Å, 1547 independent ($R_{int} = 0.0623$) reflections, 132 refined parameters, $R = 0.0558$, $wR2 = 0.1565$, max (min) residual electron density 0.631 (−0.538) e Å^{-3}.

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[10] For unknown reasons we were not able to reproduce the original protocol for the preparation of **2** from **6**. In our hands a maximum yield of 25% for **2** was obtained by thoroughly following the literature procedure [9]. After considerable experimentation, we succeeded in the preparation by the procedure given in the Experimental Section of this work.
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[13] CCDC-218288 ((−)-**10**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Center, 12 Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033 or e-mail: deposit@ccdc.cam.ac.uk).

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