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Martin Schueler [a] , Holger Zorn [b] , Alexandra M. Z. Slawin [a] & Ralf G. Berger [b]

[a] University of St Andrews , North Haugh, St Andrews, Scotland

[b] Institute of Food Chemistry , University of Hannover , Wunstorfer Str. 14, Hannover, D-30453, Germany

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Synthesis of α-Hydroxy Ketones from Terpene Aldehydes

Martin Schueler,[1] Holger Zorn,[2] Alexandra M. Z. Slawin,[1] and Ralf G. Berger[2,*]

[1]University of St Andrews, North Haugh, St Andrews, Scotland
[2]Institute of Food Chemistry, University of Hannover, Hannover, Germany

ABSTRACT

Unsymmetrically substituted α-hydroxy ketones possessing isoprenoid units within the molecule were synthesised from commercially available terpene aldehydes. The synthesis was applicable to α,β-unsaturated aldehydes and afforded the respective α-hydroxy-methyl ketones in overall good yield. Tautomerisation of these products did not occur under the conditions of reaction but was observed upon heating. Diastereoisomeric α-hydroxy ketones have been resolved, and X-ray analysis on one of these

*Correspondence: Ralf G. Berger, Institute of Food Chemistry, University of Hannover, Wunstorfer Str. 14, Hannover, D-30453, Germany; E-mail: rg.berger@lci.uni-hannover.de.

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analogues allowed for the elucidation of the stereochemistry after conversion into its camphanate ester.

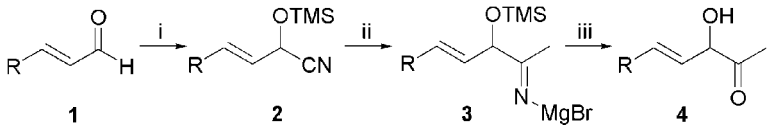
Key Words: Acyloins; α-Hydroxy ketones; Terpene aldehydes; Cyanohydrin trimethylsilyl ethers; Copper salt catalysis; Nitriles; Grignard reaction; Camphanates; Tautomerisation.

INTRODUCTION

α-Hydroxy ketones (acyloins) are of general interest as building blocks in organic synthesis,[1] and many of them have been found to display biological activity.[2–4] Several chemical methods were developed to synthesise both symmetrical and unsymmetrical acyloins. The most efficient routes to such compounds involve the "umpolung" reactions via cyanohydrins or dithioketals, which have been reviewed extensively.[5–7] Alternatively, unsymmetrical aliphatic and aromatic acyloins were obtained by nucleophilic addition of an organometallic reagent to the nitrile group of cyanohydrins.[8] These compounds, which in turn are useful intermediates for the synthesis of β-amino alcohols and carboxylic acid derivatives, are obtained readily from their respective aldehydes, and methods for their stereoselective formation are available.[9] We herein report on the application of this methodology to α,β-unsaturated aldehydes, which gave rise to some novel acyloins. The products containing various isoprenoid units within the molecule were used as reference substances for a related biosynthetic project[10] and are being evaluated as precursors in the synthesis of novel odour active pyrazines.[11]

RESULTS AND DISCUSSION

Cyanohydrin trimethylsilyl ethers are useful intermediates in the synthesis of acyloins, since protection of the hydroxyl group allows for a nucleophilic attack of an organometallic reagent at the nitrile functionality. The protected cyanohydrins are obtained readily by the direct conversion of an aldehyde with trimethylsilyl cyanide in the presence of Lewis acids or bases. Under basic conditions, the reaction presumably proceeds via a hypervalent transition state of the silicon reagent, in which the nucleophilicity of the cyanide ion is increased strongly.[12] We have applied this reaction to α,β-unsaturated aldehydes **1** using a catalytic amount of triethylamine for activation. As expected, 1,2-addition of trimethylcyanide prevails in the reaction and in all cases, the respective cyanohydrin trimethylsilyl ethers **2** were obtained in essentially quantitative yields.



Scheme 1. Reagents and conditions: (i) 1.1 eq. TMSCN, 10 mol% Et_3N, CH_2Cl_2, 2 hr, 25°C, 95–98%; (ii) 1.1 eq. CH_3MgBr, Et_2O, 6 hr, reflux; and (iii) 4 N HCl, 1–2 hr, 25°C, 80–90%.

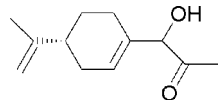
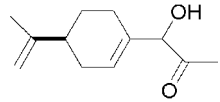
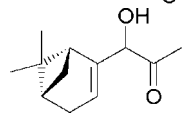
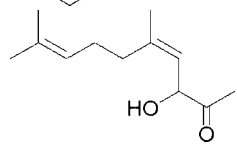
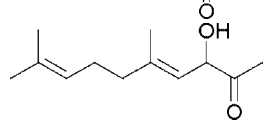
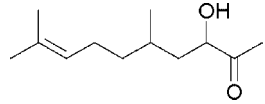
The cyanohydrin trimethylsilyl ethers were subsequently subjected to a Grignard reaction to achieve a nucleophilic addition of methylmagnesium bromide onto the nitrile group of **2**. In contrast to lithiumorganic species which yield tertiary alcohols when reacted with aldehydes,[8,13] the Grignard reagent does not facilitate a second attack on the ketimine salt **3**. Thus, acyloins **4** were obtained after acidic hydrolysis of the intermediate ketimine salt. However, the yield of the reaction generally remained low, even at elevated temperatures. Furthermore, the formation of significant amounts of a byproduct, identified as the deprotected cyanohydrin, became a major drawback in the reaction as its separation from the acyloins **4** by flash chromatography was time-consuming.

Clearly, these byproducts were formed upon hydrolysis of unreacted cyanohydrin trimethylsilyl ethers **2**, and thus result from the low reactivity of the nitrile to nucleophilic attack by the Grignard reagent. In the course of our investigation, we found that the reaction was rendered synthetically useful if copper(I) bromide was added to the reaction mixture. This allowed for complete conversion of the cyanohydrin trimethylsilyl ethers **2** and gave rise to the ketimine salts **3** in a comparably short reaction time. Formation of the aforementioned byproduct was not observed under these conditions and the acyloins **4a–f** were obtained in overall good yields (Table 1).

It has been reported previously[14] that copper(I) salts enhance strongly the reactivity of bulky Grignard reagents to nitriles. The origin of this activation is not clear but may be explained by an increased electrophilicity of the nitrile carbon due to copper coordination.

Transfer of an acyl unit onto an aldehyde results in the formation of a new chiral centre. When optically active aldehydes **1a–c** and **f** were used as substrates, the diastereoisomeric acyloins **4a–c** and **f** were formed in a 1 : 1 ratio. Conversion of neral and geranial gave racemic mixtures of acyloins **4d** and **4e**, respectively. Apart from the citronellal derived compounds (1*R*)-**4f** and (1*S*)-**4f**, the diastereoisomers could be separated by flash chromatography on silica gel. In order to determine their absolute configuration, the acyloins were converted into their corresponding camphanates (Fig. 1).

Table 1. Isoprenoid acyloins obtained from terpene aldehydes and copper(I) bromide catalysis.

Entry	Aldehyde	Acyloin	Isolated yield (%)
A	(+)-Perillaaldehyde		88
B	(−)-Perillaaldehyde		85
C	(−)-Myrtenal		89
D	Neral		82
E	Geranial		84
F	(+/−)-Citronellal		90

The compound **6b**, derived from the acyloins **4a**, gave crystals suitable for x-ray analysis, and thus the stereochemistry of both diastereoisomers of **4a** was unambiguously assigned (Fig. 2).

The absolute configuration of the acyloins (1*R*)-**4b** and (1*S*)-**4b** was resolved as well, since (1*S*)-**4b** is the mirror image to (1*R*)-**4a**, and similarly,

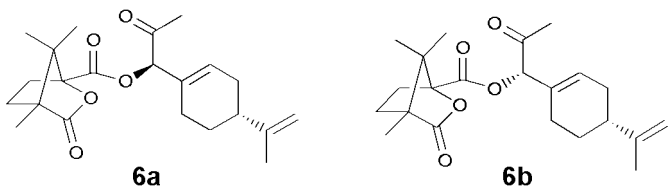


Figure 1. Camphanates **6a** and **6b** of diastereoisomeric acyloins (1*R*)-**4a** and (1*S*)-**4a** derived from (1*S*)-(−)-camphanoyl chloride.

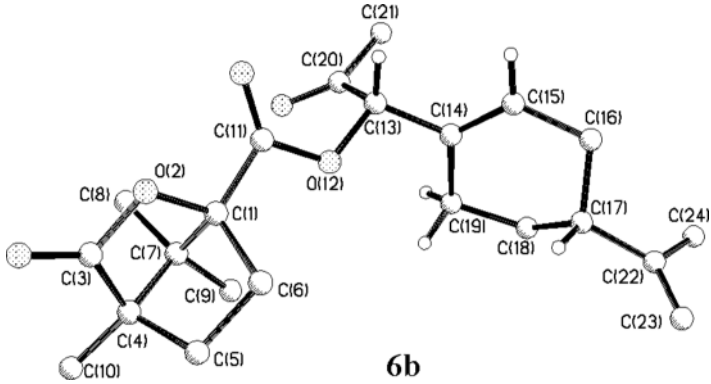


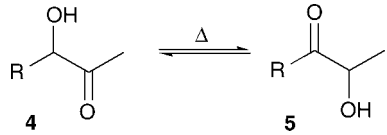
Figure 2. Ball and stick drawing of the x-ray generated molecular structure of the camphanate **6b**. The hydroxyl substituted carbon C(13) is referred to as the C(1) of acyloins **4a**.

(1*R*)-**4b** to (1*S*)-**4a**. Hence, these sets of acyloins represent enantiomers and therefore NMR and MS data of all four stereoisomers could be assigned. Although the diastereoisomeric acyloins (1*R*)-**4c** and (1*S*)-**4c** were separated readily by flash chromatography, these compounds and their respective camphanate esters did not give crystals suitable for x-ray spectroscopy.

Nevertheless, we feel justified to infer the stereochemistry of these diastereoisomers on the basis of their optical rotation, since structurally related acyloins with a negative sign of optical rotation have been reported to have an R-configuration.[15–18]

In relation to our biosynthetic project, it was of interest to evaluate the stability of the newly formed stereogenic centre and the liability of these compounds towards tautomerisation. An attempt to purify acyloin **4f** by distillation led to the formation of its tautomer **5f** (Sch. 2).

Moreover, when the specified acyloins were analysed by means of GC–MS, mixtures of both tautomers were observed for the aliphatic acyloins **4d–f**. Although the tautomers **5a–f** could not be detected in acidic or basic solution by means of NMR, the formation of **5d–f** indicates that a thermal



Scheme 2. Thermal tautomerisation of 1-hydroxy-2-oxopropanes **4d–f** results in the formation of their corresponding 2-hydroxy-1-oxopropanes **5d–f**.

tautomerisation occurs readily for aliphatic acyloins at high temperatures. The degree of tautomerisation was found to be highly dependent on the nature of the substrate, and the absence of the alicyclic tautomers **4a–c** may possibly be attributed to the limits of GC–MS detection.

EXPERIMENTAL

Reagents and solvents were purchased from Fluka and Merck. All solvents were dried prior to use and kept over 4 Å molecular sieves. NMR spectra were recorded with either a Bruker AV-400 (400.13 MHz ^{1}H; 100.61 MHz ^{13}C) or a Varian Gemini 300 MHz (299.98 ^{1}H; 75.43 ^{13}C) spectrometer. GC–MS analyses were performed on an Agilent 6890 gas chromatograph (split-injection) connected to an Agilent 5973 mass-selective detector equipped with an Optima 5-MS column (Macherey&Nagel; 30 m × 0.25 mm; ID, 0.25 μm). IR spectra were obtained using a Perkin Elmer Paragon 1000 FT-IR instrument. Optical rotations were determined on an AA-1000 polarimeter (Optical Activity Ltd). A GallenKamp GRIFFIN MPA350.BM2.5 melting point apparatus was used to provide melting points, which are uncorrected.

General Procedure for the Synthesis of Acyloins

To a solution of the aldehyde (5 mmol) in dry dichloromethane (10 mL) was added trimethylsilyl cyanide (0.75 mL, 6 mmol) via syringe at 0°C. Triethylamine (0.07 mL, 0.5 mmol) was added to the reaction mixture, which was then stirred at room temperature for 2 hr under nitrogen. The solvent was removed under reduced pressure and the residue dissolved in dry diethylether (20 mL). This mixture was added to a preformed solution of copper bromide (90 mg, 0.6 mmol) and 3 M methylmagnesium bromide solution in diethylether (2 mL, 6 mmol) under a static atmosphere of nitrogen. The reaction mixture was refluxed for 6 hr, then cooled to room temperature, and made up in ice-water (10 mL). Hydrochloric acid (10 mol%, 10 mL) was added slowly and the mixture was stirred vigorously for 1–2 hr. The phases were separated and the water layer extracted with EtOAc (3 × 10 mL). The combined organic phases were washed with water, saturated sodium bicarbonate solution, and saturated sodium chloride solution before being dried over sodium sulphate. The solvent was removed under reduced pressure and the product was purified by flash chromatography (hexane/ethylacetate 4 : 1).

(1*R*)-1-Hydroxy-1-[(4′*R*)-4′-isopropenyl-1-cyclohexen-1-yl]-2-propanone, (*R*)-4a. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 5.96 (t, $^{3}J = 2.3$, 1H, C(2′)–H), 4.73 (m, 1H, C(8′)–H), 4.71 (m, 1H, C(8′)–H), 4.52 (s, 1H, C(1)–H),

3.82 (d, $^3J = 4.36$, 1H, OH), 2.18 (s, 3H, C(3)–H_3), 2.24–1.60 (m, 7H, C(3′)–H_2, C(4′)–H, C(5′)–H_2, C(6′)–H_2), 1.73 (s, 3H, C(9)–H_3). ^{13}C-NMR δ (100 MHz, $CDCl_3$): 208.4 (C═O), 149.2 C(7′), 109.0 C(8′), 135.0 C(1′), 129.4 C(2′), 82.2 C(1), 41.22 C(4′), 30.82 C(6′), 27.18 C(5′), 24.71 C(3), 23.16 C(3′), 20.62 C(9′). MS (EI, 70 eV): m/z 194 ($M^{+\bullet}$, 3), 151 (100), 149 (46), 45 (10), 43 (72). IR ν (film, cm^{-1}): 3447 (br), 1713. The analytical data matched those of enantiomeric (*S*)-**4b**.

(1*S*)-1-Hydroxy-1-[(4′*R*)-4′-isopropenyl-1-cyclohexen-1-yl)-2-propanone, (*S*)-4a. ^{1}H-NMR δ (400 MHz, $CDCl_3$): 5.95 (m, 1H, C(2′)–H), 4.74 (m, 1H, C(1′)–H), 4.68 (m, 1H, C(1′)–H); 4.51 (d, $^3J = 4.45$, 1H, C(1)–H), 3.77 (d, $^3J = 4.36$, 1H, OH), 2.15 (s, 3H, C(3)–H_3), 2.24–1.60 (m, 7H, C(3′)–H_2, C(4′)–H, C(5′)–H_2, C(6′)–H_2), 1.73 (s, 3H, C(3′)–H_3). ^{13}C-NMR δ (100 MHz, $CDCl_3$) 208.6 C(2), 149.0 C(7′), 108.9 C(8′), 134.8 C(1′), 128.8 C(2′), 82.5 C(1), 40.14 C(4′), 30.57 C(6′), 26.98 C(5′), 24.84 C(3), 23.08 C(3′), 20.85 C(9′). MS (EI, 70 eV): m/z 194 ($M^{+\bullet}$, 3), 151 (100), 149 (40), 45 (12), 43 (90). IR ν (film, cm^{-1}): 3460 (br), 1713. The analytical data matched those of enantiomeric (*R*)-**4b**.

(1*R*,1′*R*)-1-(6,6-Dimethyl-bicyclo[3.1.1]hept-2-en-2-yl)-1-hydroxy-2-propanone, (1*R*)-4c. $[\alpha]_D = -291^\circ$ ($CHCl_3$, $c = 0.520$). ^{1}H-NMR δ (400 MHz, $CDCl_3$): 5.75 (s, 1H, C(3′)–H), 4.53 (d, $^3J = 3.6$, 1H, C(1)–H), 3.66 (d, $^3J = 4.2$, 1H, OH), 2.42–2.37 (m, 1H, C(7′)–H), 2.35 (t, $^3J = 2.9$, 2H, C(4′), 2.16 (s, 3H, C(3)–H_3), 2.14–2.09 (m, 1H, C(5′)–H), 1.92 (td, $J = 5.5$, $J = 1.5$, 1H, C(1′)–H), 1.25 (s, 3H, C(6′)–CH_3), 1.05 (d, $^2J = 8.7$, 1H, C(7′)–H), 0.85 (s, 3H, C(6′)–CH_3). ^{13}C-NMR δ (100 MHz, $CDCl_3$): 208.1 (C═O), 144.5 C(2′), 124.8 C(3′), 80.7 C(1), 41.28 C(1′), 40.78 C(5′), 38.09 C(6′), 32.11 C(7′), 31.67 C(4′), 25.96 C(9′), 25.04 C(3), 21.06 C(8′). MS (EI, 70 eV): m/z 194 ($M^{+\bullet}$, 0.5), 151 (13), 149 (2), 45 (10), 43 (100). IR ν (film, cm^{-1}): 3474 (br), 1716.

(1*S*,1′*R*)-1-(6,6-Dimethyl-bicyclo[3.1.1]hept-2-en-2-yl)-1-hydroxy-2-propanone, (1*S*)-4c. $[\alpha]_D = +297^\circ$ ($CHCl_3$, $c = 0.520$). ^{1}H-NMR δ (400 MHz, $CDCl_3$): 5.75 (s, 1H, C(3′)–H), 4.60 (d, $^3J = 3.2$, 1H, C(1)–H), 3.75 (d, $^3J = 4.56$, 1H, OH), 2.49–2.43 (m, 1H, C(7′)–H), 2.35 (dt, $^2J = 18.2$, $^3J = 2.46$, 2H, C(4′), 2.18 (s, 3H, C(3)–H_3), 2.15–2.10 (m, 1H, C(5′)–H), 2.14–2.06 (m, $J = 1.5$, 1H, C(1′)–H), 1.28 (s, 3H, C(6′)–CH_3), 1.22 (d, $^2J = 8.76$, 1H, C(7′)–H), 0.82 (s, 3H, C(6′)–CH_3). ^{13}C-NMR δ (100 MHz, $CDCl_3$): 207.4 (C═O); 144.6 C(2′), 124.3 C(3′), 81.0 C(1), 41.66 C(1′), 40.51 C(5′), 37.54 C(6′), 32.01 C(7′), 31.47 C(4′), 26.01 C(9′), 25.34 C(3), 21.35 C(8′). MS (EI, 70 eV): m/z 194 ($M^{+\bullet}$, 0.5), 151 (13), 149 (2), 45 (10), 43 (100). IR ν (film, cm^{-1}): 3456 (br), 1716.

(*Z*)-3-Hydroxy-5,9-dimethyl-deca-4,8-dien-2-one, (*R*,*S*)-4d. A commercially available mixture of neral and geranial was used as starting material in the synthesis, and the E- and Z-isomers **4d** and **4e** were then separated by flash

chromatography on silica gel. ^{1}H-NMR δ (400 MHz, $CDCl_3$): 5.75 (m, $^3J = 7.0$, 1H, C(8)–H), 4.95 (d, $^3J = 10.0$, 1H, C(4)–H), 4.75 (d, $^3J = 10.0$, 1H, C(3)–H), 3.58 (d, $J = 2.9$, 1H, OH), 2.2 (m, 2H, C(6)–H), 2.13 (m, 2H, C(7)–H), 2.1 (s, 3H, C(1)–H_3), 1.75 (d, $^4J = 1.4$, 3H, C(5)–CH_3), 1.63 (d, $^4J = 1.0$, 3H, C(10)–H_3), 1.57 (s, 3H, C(9)–CH_3). ^{13}C-NMR δ (100 MHz, $CDCl_3$): 208.4 C(2), 143.8 C(5), 132.5 C(9), 123.4 C(8), 121.8 C(4), 74.3 C(3), 32.5 C(6), 26.4 C(7), 25.7 C(10), 25.1 (1), 23.4 C(5)–CH_3, 17.6 C(9)–CH_3. MS (EI, 70 eV): m/z 196 ($M^{+\bullet}$, 0.5), 153 (4), 151 (36), 69 (100), 45 (10), 43 (12).

(*E*)-3-Hydroxy-5,9-dimethyl-deca-4,8-dien-2-one, (*R*,*S*)-4e. ^{1}H-NMR δ (400 MHz, $CDCl_3$): 5.03 (m, 1H, C(8)–H), 5.0 (dq, $^3J = 9.40$, $^4J = 1.3$, 1H, C(4)–H), 4.8 (dd, $^3J = 9.4$, 3.4, 1H, C(3)–H), 3.7 (d, $^3J = 4.1$, 1H, OH), 2.13 (s, 3H, C(1)–H_3), 2.12–2.05 (m, 4H, C(7)–H_2, C(6)–H_2), 1.83 (d, $^4J = 1.4$, 3H, C(5)–CH_3), 1.65 (d, $^4J = 1.0$, 3H, C(10)–H_3), 1.58 (s, 3H, C(9)–CH_3). ^{13}C-NMR δ (100 MHz, $CDCl_3$): 208.3 C(2), 143.0 C(5), 131.9 C(9), 123.5 C(8), 121.6 C(4), 74.8 C(3), 39.6 C(6), 26.1 C(7), 25.6 C(10), 24.9 (1), 17.6 C(9)–CH_3, 16.9 C(5)–CH_3. MS (EI, 70 eV): m/z 196 ($M^{+\bullet}$, 0.5), 153 (32), 151 (29), 69 (100), 45 (9), 43 (39).

3-Hydroxy-5,9-dimethyl-dec-8-en-2-one, (*R*,*S*)-4f. ^{1}H-NMR δ (300 MHz, $CDCl_3$): 5.12, 5.08 (m, 1H, C(8)–H), 4.2 (m, 1H, C(3)–H), 2.2 (s, 3H, C(1)–H_3), 2.0 (m, 2H, C(7)–H_2), 1.8 (m, 2H, C(4)–H), 1.68 (m, 3H, C(9)–CH_3), 1.62, 1.60 (s, 3H, C(10)–H_3), 1.5–1.1 (m, 3H, C(3)–H, C(6)–H_2), 1.0, 0.96 (d, $J = 6.6$ Hz, 3H, C(5)–CH_3). ^{13}C-NMR δ (75 MHz, $CDCl_3$): 210.4 (C=O), 131.8 C(9), 124.9, 124.8 C(8), 75.5, 75.2 C(3), 41.5, 41.3 C(7), 38.3, 38.1 C(4), 29.8, 29.5 C(5), 25.7 C(1), 25.8, 25.7 C(6), 25.2, 25.1 C(5)–CH_3, 20.3 C(10), 17.6 C(10)–CH_3. MS (EI, 70 eV): m/z 198 ($M^{+\bullet}$, 3), 155 (3), 153 (5), 69 (100), 45 (24), 43 (85). IR ν (film, cm^{-1}): 3404 (br), 1703.

(*Z*)-2-Hydroxy-5,9-dimethyl-deca-4,8-dien-3-one, (*R*,*S*)-5d. MS (EI, 70 eV): m/z 196 ($M^{+\bullet}$, 0.2), 153 (1), 151 (40), 69 (100), 45 (13), 43 (12).

(E)-2-Hydroxy-5,9-dimethyl-deca-4,8-dien-3-one, (*R*,*S*)-5e. MS (EI, 70 eV): m/z 196 ($M^{+\bullet}$, 0.5), 153 (3), 151 (23), 69 (100), 45 (5).

2-Hydroxy-5,9-dimethyl-dec-8-en-3-one, (*R*,*S*)-5f. MS (EI, 70 eV): m/z 198 ($M^{+\bullet}$, 2), 155 (1), 153 (3), 69 (100), 45 (53), 43 (48).

Synthesis of Camphanate Esters

To a solution of acyloin **4a** (110 mg, 0.57 mmol) in pyridine (1 mL) was added (*S*)-(−)-camphanoyl chloride (125 mg, 1 mmol) at −20°C. The reaction mixture was stirred at 0°C for 8 hr and the resulting suspension was then diluted with ether (1 mL). This was quenched into ice-water (2 mL), the layers were separated, and the organic phase washed with saturated aqueous solution of sodium bicarbonate, water, and brine. The solvent was

removed under reduced pressure and the diastereoisomers were separated by flash chromatography (hexane/ethylacetate, 9 : 1).

(1*S*)-Camphanate ester 6a. Yield 68%. M.p.: 86°C. ^{1}H-NMR δ (300 MHz, $CDCl_3$): 6.04 (d, 1H, C(15)–H), 5.52 (s, 1H, C(13)–H), 4.75, (m, 1H, C(23)–H), 4.69 (m, 1H, C(23)–H), 2.5–1.4 (m, 11H, C(5)–H_2, C(6)–H_2, C(16)–H_2, C(17)–H, C(18)–H_2, C(19)–H_2), 2.16 (s, 3 H, C(21)–H_3), 1.73 (s, 3 H, C(24)–H_3); 1.15 (s, 3 H, C(7)–CH_3), 1.12 (s, 3 H, C(4)–CH_3), 1.03 (s, 3 H, C(7)–CH_3). MS (EI, 70 eV): m/z 374 ($M^{+\bullet}$, 1). IR ν (film, cm^{-1}): 1791, 1748, 1725.

(1*S*)-Camphanate ester 6b. M.p. 88°C. ^{1}H NMR δ (300 MHz, $CDCl_3$): 6.04 (d, 1H, C(15)–H), 5.52 (s, 1H, C(13)–H), 4.75, (m, 1H, C(23)–H), 4.69 (m, 1H, C(23)–H), 2.5–1.4 (m, 11H, C(5)–H_2, C(6)–H_2, C(16)–H_2, C(17)–H, C(18)–H_2, C(19)–H_2), 2.16 (s, 3H, C(21)–H_3), 1.73 (s, 3H, C(24)–H_3), 1.15 (s, 3H, C(7)–CH_3), 1.12 (s, 3H, C(4)–CH_3), 1.03 (s, 3H, C(7)–CH_3). MS (EI, 70 eV) m/z 374 ($M^{+\bullet}$, 5). IR ν (film, cm^{-1}): 1790, 1748, 1726.

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