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Efficient and practical synthesis of both enantiomers of 6-silyloxy-3-pyranone derivatives

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Abstract

Lipase catalyzed kinetic resolution of racemic *cis*-6-(*tert*-butyldimethylsilyloxy)-3,6-dihydro-2*H*-pyran-3-ol (*rac*)-**1** was achieved in high enantiomeric excess. Transesterification of (*rac*)-**1** with vinylacetate in ^{t}BuOMe yielded the alcohol (3*S*,6*R*)-**1** in 99.0% ee, whereas (3*R*,6*S*)-**1** was obtained, in 99.0% ee, by the lipase catalyzed ester hydrolysis of acetate (3*R*,6*S*)-**2**, which was obtained along with the transesterification. Both (3*S*,6*R*)-**1** and (3*R*,6*S*)-**1** were subjected to oxidation to provide the corresponding 6-silyloxy-3-pyranone (6*R*)-**3** and (6*S*)-**3**, respectively. Application to the synthesis of **7**, which is the key intermediate of asymmetric synthesis of pseudomonic acid A **9** is also described.

1. Introduction

Optically active 6-substituted-3-pyranones are attractive synthons in natural product synthesis due to their multifunctional nature and diverse possibilities for stereoselective transformations.[1a] Usually, optically active 6-substituted-3-pyranones are prepared from sugar-derived glycals via the Ferrier rearrangement.[2a,b] However in the case of substrates with no substituent at the C-2 position,[†] such as D-arabinose or D-xylose-derived glycals, Ferrier reaction shows poor stereoselectivity and, as a result, tedious separation of diastereomers cannot be avoided.[2c] On the other hand, racemic 6-substitued-3-pyranones are readily accessible from inexpensive furfuryl alcohols. Therefore, resolution methods, especially enzyme-catalyzed reactions, are more preferable in these cases. Although Feringa and co-workers have already reported the lipase catalyzed resolution of racemic 6-acetoxy-3-pyranone,[1b,c] the enantiomeric excess (ee) of the (*S*)-enantiomer is only moderate. We wish to report here an efficient and practical route to the enantiomerically pure 6-*tert*-butyldimethylsilyloxy-3-pyranones (*R*)- and (*S*)-**3** via a lipase catalyzed resolution (Scheme 1).

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[†] Numbering of the products follows pyranone numbering.

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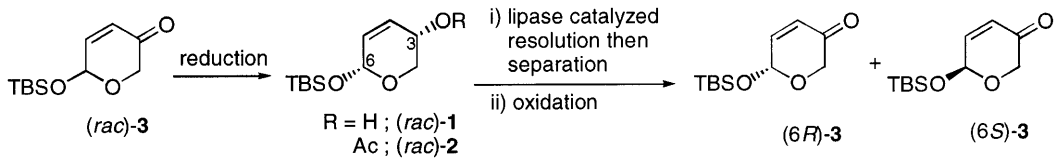
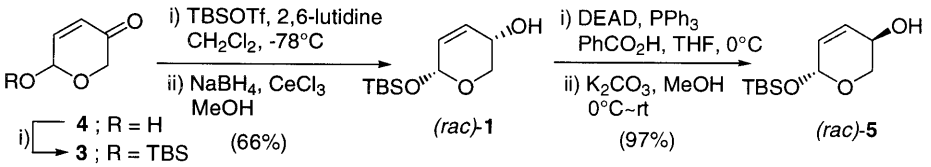


Scheme 1.

2. Results and discussion

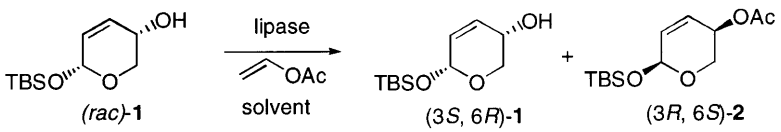
Since lipase catalyzed kinetic resolution of secondary alcohols is a well known procedure, we applied this methodology to the resolution of racemic 6-substituted-3-pyranols. In order to investigate the effect of the relative configuration of the 3- and 6-positions, (*rac*)-**1** and (*rac*)-**5** were prepared stereoselectively from the known pyranone **4**[3] (Scheme 2).



Scheme 2.

First we examined several commercially available lipases for their activity and stereoselectivity in the transesterification of (*rac*)-**1**. The results are shown in Table 1.

Table 1
Lipase catalyzed transesterification of (*rac*)-**1**[a]



Entry	Lipase	Solvent	Temp. (°C)	Time (h)	Alcohol-**1**		Acetate-**2**		*E*-value[4]
					Yield[b] (%)	% ee[d]	Yield[b] (%)	% ee[d]	
1	OF	^{t}BuOMe	rt	192	NR	–	NR	–	–
2	AY	^{t}BuOMe	rt	216	96[c]	ND	4[c]	ND	–
3	PPL	^{t}BuOMe	rt	192	97[c]	ND	3[c]	ND	–
4	Chirazyme	^{t}BuOMe	rt	0.5	27	90.8	73	31.2	5
5	PS	^{t}BuOMe	rt	120	40	97.4	52	77.6	29
6	AK	^{t}BuOMe	rt	29	40	95.3	52	77.6	28
7	AK	^{t}BuOMe	5	84	42	99.0	54	78.4	42
8	AK	CH_3CN	5	84	18	ND	82	ND	–
9	AK	CH_2Cl_2	5	84	25[c]	ND	75[c]	ND	–

[a] All reactions were carried out with vinyl acetate (2 equiv.), MS 4 Å (45 mg/mmol) and lipase (45 mg/mmol) in various solvents (22 mL/mmol).

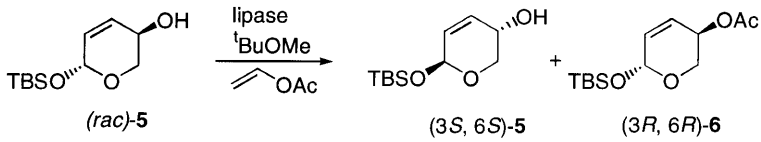
[b] Isolated yield after column chromatography.

[c] Conversion yield determined by ^{1}H NMR (300 MHz).

[d] Determined by HPLC after transformation into **3**. NR, no reaction; ND, not determined.

Among the lipases examined, lipases PS and AK showed good activity and stereoselectivity ($E=29$ and 28, respectively), while lipases OF, AY, PPL, and Chirazyme gave unsatisfactory results. Concerning the solvents, ^{t}BuOMe proved to be the solvent of choice. When the reaction using lipase AK was performed at 5°C, the highest selectivity was achieved ($E=42$) and (3*S*,6*R*)-**1** of 99.0% ee was obtained in 42% yield.

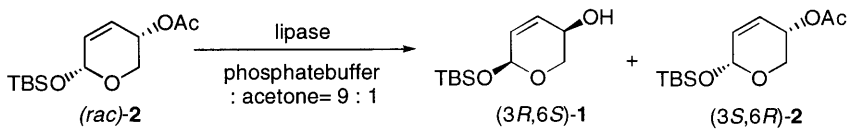
When (*rac*)-**5** was subjected to similar reaction conditions, the selectivity decreased ($E=13$) and the yield and ee of (3*S*,6*S*)-**5** were 47.0 and 83.1% ee, respectively (Scheme 3). It is noteworthy that the lipase preferentially acylated (3*R*)-isomers regardless of the C-6 configuration and the *cis*-isomer **1** is a better substrate than the *trans*-isomer **5**.



Scheme 3.

Since the (6*S*)-isomer could not be obtained in satisfactory yield and ee in the transesterification, we turned our attention next to asymmetric hydrolysis of the acetate (*rac*)-**2** in phosphate buffer–acetone solution (9:1 v/v) (Table 2). Lipase AK again showed excellent selectivity to give the (3*R*,6*S*)-**1** in 92.2% ee (50% yield) at rt ($E=106$) and 96.3% ee (26% yield) at 5°C, respectively. The selectivity was lowered slightly ($E=71$) when lipase PS was employed.

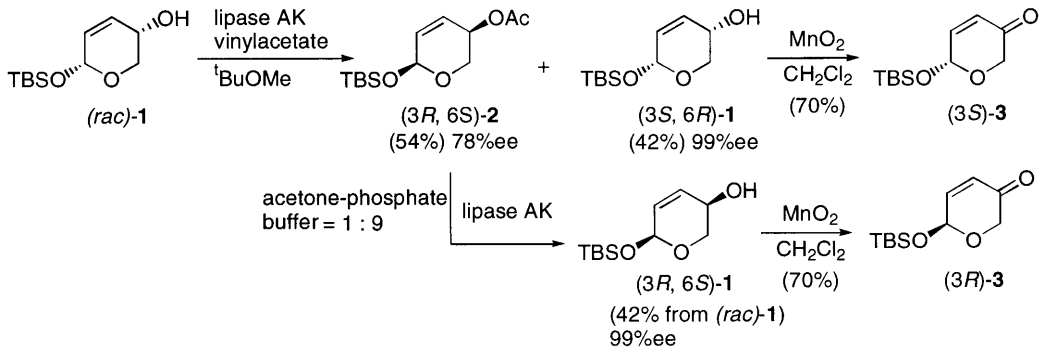
Table 2
Lipase catalyzed ester hydrolysis of (*rac*)-**2**[a]



Entry	Lipase	Temp. (°C)	Time (h)	Alcohol-**1**		Acetate-**2**		*E*-value
				Yield[b] (%)	% ee[c]	Yield[b] (%)	% ee[c]	
1	AK	rt	15	50	92.2	44	97.3	106
2	AK	5	24	26	96.3	66	82.6	92
3	PS	rt	111	40	86.9	39	98.7	71

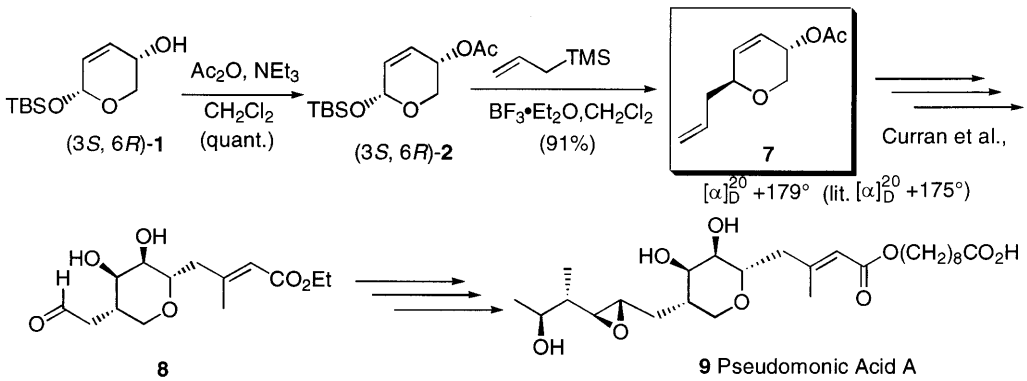
[a] All reactions were carried out with lipase (90 mg/mmol) in phosphate buffer (pH 7.0, 1/15 mmol)–acetone = 9:1 (10 mL/mmol).
[b] Isolated yield after column chromatography.
[c] Determined by HPLC after transformation into **3**.

Practically, a combination of transesterification and ester hydrolysis was effective. Thus both (3*S*,6*R*)- and (3*R*,6*S*)-**1** were obtained with 99.0% ee in satisfactory yield (Scheme 4). Finally, oxidation with manganese dioxide gave 6-*tert*-butyldimethylsilyloxy-3-pyranones (6*R*)-**3** and (6*S*)-**3**, respectively.



Scheme 4.

The absolute configuration of the products was determined by transformation of (3*S*,6*R*)-**1** into the key intermediate of the asymmetric synthesis of pseudomonic acid A[5] (Scheme 5). Thus, acetylation of (3*S*,6*R*)-**1** to (3*S*,6*R*)-**2** followed by treatment with allylsilane in the presence of $BF_3{\cdot}OEt_2$ yielded the 3,6-*trans*-dihydropyran **7**. The analytical data including the specific rotation of **7** were identical with the reported ones.[6] At this point the absolute configurations of the resolution products were determined unambiguously.



Scheme 5.

In conclusion, both enantiomers of 6-*tert*-butyldimethylsyilyloxy-3-pyranones **3** have been obtained in high enantiomeric excess by employing a lipase-mediated resolution method. Utilization of optically active pyranones for stereoselective synthesis of natural products is currently under investigation.

3. Experimental

3.1. General

Melting points were determined using a Büchi 535 melting point apparatus and are uncorrected. Optical rotations were measured on a Horiba SEPA-200 high sensitive polarimeter. IR

spectra were obtained with an Analect FT-IR spectrophotometer. ^{1}H NMR spectra were measured with a Varian Gemini-300 spectrometer. Mass spectra were recorded using a Finnigan MAT SSQ7000C (APCI) or a Jeol JMS-HX 100 (FAB) mass spectrometer. Elemental analysis was performed on a Perkin–Elmer 2400 elemental analyzer. All reactions were monitored by TLC on silica gel 60 GF_{254} (Merck). Column chromatography was performed on silica gel 60N (spherical, neutral) (100–210 μm, Kanto). Flash chromatography was performed on silica gel 60N (spherical, neutral) (40–100 μm, Kanto). In general, reactions were carried out in dry solvents under an argon atmosphere. Lipases OF, AY, PS, and AK were purchased from Amano; PPL from Sigma; Chirazyme® from Roche.

3.2. *(±)-6-*tert-*Butyldimethylsilyloxy-2*H-*pyran-3(6*H*)-one; (*rac*)-**3**

To a cooled (−78°C) solution of (±)-6-hydroxy-2*H*-pyran-3(6*H*)-one[3] (**4**, 4.13 g, 36.1 mmol) in CH_2Cl_2 (100 mL) were added 2,6-lutidine (6.31 mL, 54.2 mmol) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (10.2 mL, 43.4 mmol), and the mixture was slowly warmed to 0°C. After the mixture was stirred for 30 min at 0°C, the reaction was quenched with H_2O (20 mL). The organic layer was separated and washed with 10% citric acid and brine. The organic extract was dried ($MgSO_4$) and concentrated in vacuo. Purification of the residue by column chromatography (1:8 EtOAc–hexane→1:4 EtOAc–hexane) gave 6.77 g (82%) of **3** as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.17 (s, 6H, –$SiCH_3$), 0.92 (s, 9H, –^{t}Bu), 4.08 (dd, 1H, J=16.8, 0.5 Hz, –CH_2), 4.51 (d, 1H, J=16.8 Hz, –CH_2), 5.53 (d, 1H, J=3.1 Hz, –CH), 6.08 (d, 1H, J=10.3, –C*H*=CH), 6.86 (dd, 1H, J=10.3, 3.1 Hz, –CH=C*H*); IR (neat) 1707 cm^{-1}; MS (FAB, +$AcONH_4$) m/z 246 $(M+NH_4)^+$; anal. calcd for $C_{11}H_{20}O_3Si$: C, 57.85; H, 8.83. Found: C, 57.54; H, 8.66.

3.3. cis-*(±)-6-(*tert-*Butyldimethylsilyloxy)-3,6-dihydro-2*H-*pyran-3-ol; (*rac*)-**1**

To a cooled (−20°C) solution of **3** (27.85 g, 119.8 mmol) and $CeCl_3 \cdot 7H_2O$ (44.6 g, 119.8 mmol) in MeOH (500 mL) was added portionwise $NaBH_4$ (4.53 g, 119.8 mmol). After the mixture was stirred for 30 min at −20°C, the reaction was quenched with acetone (50 mL) and stirred at rt for 30 min. H_2O was added to the mixture, which was extracted with CH_2Cl_2. The organic layer was washed with H_2O and brine, dried ($MgSO_4$), and concentrated in vacuo. Purification of the residue by flash chromatography (1:4 EtOAc–hexane) gave 22.3 g (81%) of **1** as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.14 (s, 6H, –$SiCH_3$), 0.91 (s, 9H, –^{t}Bu), 1.67 (d, 1H, J=9.2 Hz, exchange with D_2O, –OH), 3.72–3.80 (m, 2H, –CH_2), 4.14 (m, 1H, –CH), 5.25 (m, 1H, –CH), 5.75 (ddd, 1H, J=10.3, 2.2, 1.7 Hz, –C*H*=CH), 5.95 (dd, 1H, J=10.3, 2.8 Hz, –CH=C*H*); IR (neat) 3200–3550 cm^{-1}; MS (APCI, +$AcONH_4$) m/z 248 $(M+NH_4)^+$; anal. calcd for $C_{11}H_{22}O_3Si$: C, 57.35; H, 9.63. Found: C, 57.58; H, 9.84.

3.4. trans-*(±)-6-(*tert-*Butyldimethylsilyloxy)-3,6-dihydro-2*H-*pyran-3-ol; (*rac*)-**5**

To a cooled (0°C) solution of **1** (1.15 g, 5.0 mmol), PPh_3 (1.44 g, 5.5 mmol) and benzoic acid (0.73 g, 6.0 mmol) in THF (30 mL) was added diethylazodicarboxylate (0.88 g, 5.5 mmol), and the mixture was stirred for 30 min at 0°C, then warmed up to rt. After 3 h, the reaction was quenched with H_2O and the mixture was extracted with EtOAc. The organic layer was washed with H_2O and brine, dried ($MgSO_4$), and concentrated in vacuo. Purification of the residue by

flash chromatography (1:9 EtOAc–hexane) gave 1.67 g (quant.) of the benzoate of **5** as a colorless oil.

To a cooled (0°C) solution of the above benzoate (1.0 g, 3.0 mmol) in MeOH (20 mL) was added K_2CO_3 (0.62 g, 4.5 mmol), and the mixture was stirred at 0°C for 3 h. After addition of H_2O (10 mL), the mixture was extracted with EtOAc. The organic layer was washed with H_2O and brine, dried ($MgSO_4$), and concentrated in vacuo. Purification of the residue by flash chromatography (1:3 EtOAc–hexane) gave 0.67 g (97%) of (*rac*)-**5** as a colorless solid: mp 39–43°C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.13 (s, 6H, –$SiCH_3$), 0.91 (s, 9H, –^{t}Bu), 1.91 (d, 1H, J=9.5 Hz, exchange with D_2O, –OH), 3.76 (ddd, 1H, J=12.3, 1.5, 1.1 Hz, –CH_2), 3.81 (m, 1H, –CH), 4.15 (dd, 1H, J=12.3, 2.6 Hz, –CH_2), 5.28 (d, 1H, J=3.1 Hz, –CH), 5.84 (dd, 1H, J=10.1, 3.1 Hz, –C*H*=CH), 6.05 (dddd, 1H, J=10.1, 5.3, 1.5, 1.1 Hz, –CH=C*H*); IR (neat) 3200–3550 cm^{-1}; MS (APCI, +$AcONH_4$) m/z 248 $(M+NH_4)^+$; anal. calcd for $C_{11}H_{22}O_3Si$: C, 57.35; H, 9.63. Found: C, 57.21; H, 9.60.

3.5. *Lipase AK mediated kinetic resolution of (rac)-**1***

Into a suspension of (*rac*)-**1** (6.62 g, 28.7 mmol), lipase AK (1.33 g) and molecular sieves 4 Å (3.0 g) in ^{t}BuOMe (250 mL) was added vinyl acetate (5.3 mL, 57.5 mmol), and the mixture was stirred at 5°C. When 56% conversion was reached (determined by ^{1}H NMR, 84 h), the mixture was filtered through a Celite pad, and the filtrate was concentrated in vacuo. Purification of the residue by flash chromatography (1:3 EtOAc–hexane) gave the alcohol (3*S*,6*R*)-**1** (2.80 g, 42%, 99.0% ee) and the acetate (3*R*,6*S*)-**2** (4.21 g, 54%, 78.4% ee) as a colorless oil. The acetate (3*R*,6*S*)-**2**, obtained above (4.21 g, 15.4 mmol), was suspended into a phosphate buffer (pH 7.0, 1/15 mmol)–acetone solution (9:1 v/v, 160 mL) and lipase AK (1.45 g) was added at 5°C. The heterogeneous mixture was stirred vigorously at 5°C for 24 h. After filtration through a Celite pad, the filtrate was extracted with EtOAc. The organic layer was washed with brine, dried ($MgSO_4$), and concentrated in vacuo. Purification of the residue by column chromatography (1:3 EtOAc–hexane) gave the alcohol (3*R*,6*S*)-**1** (2.80 g, 42% from (*rac*)-**1**, 99.0% ee) as a colorless oil (the enantiomeric excess of **1** was determined by HPLC (Chirapak AD-RH, CH_3CN/H_2O= 45/55) after transformation into **3**, vide infra).

(3*S*,6*R*)-**1**: $[\alpha]_D^{20}$=44.3 (*c* 1.02, $CHCl_3$). (3*R*,6*S*)-**1**: $[\alpha]_D^{20}$=–43.4 (*c* 0.59, $CHCl_3$). Other spectral data were in accordance with (*rac*)-**1**.

3.6. (R)-6-tert-*Butyldimethylsilyloxy*-2H-*pyran*-3(6H)-*one; (6*R*)-**3***

A mixture of (3*S*,6*R*)-**1** (687 mg, 2.95 mmol, 99.0% ee) and MnO_2 (6.8 g) in CH_2Cl_2 (70 mL) was stirred at rt for 2 h. The mixture was filtered through a Celite pad and the filtrate was concentrated in vacuo. Purification of the residue by column chromatography (1:5 EtOAc–hexane) gave 470 mg (70%) of (6*R*)-**3** as a colorless oil: $[\alpha]_D^{20}$=–63.7 (*c* 0.55, $CHCl_3$). Other spectral data were in accordance with (*rac*)-**3**.

3.7. (S)-(+)-6-tert-*Butyldimethylsilyloxy*-2H-*pyran*-3(6H)-*one; (6*S*)-**3***

(6*S*)-**3** was obtained by the same procedure as the preparation of (6*R*)-**3** using (3*R*,6*S*)-**1** as a substrate: $[\alpha]_D^{20}$=63.4 (*c* 0.27, $CHCl_3$). Other spectral data were in accordance with (*rac*)-**3**.

3.8. (3S,6R)-cis-6-(tert-Butyldimethylsilyloxy)-3,6-dihydro 2H-pyran-3-yl acetate; (3S,6R)-2

To a solution of (3*S*,6*R*)-**1** (230 mg, 1.00 mmol) and NEt_3 (0.28 mL, 2.00 mmol) in CH_2Cl_2 (4.0 mL) was added Ac_2O, and the mixture was stirred at rt for 6 h. MeOH (0.5 mL) was added, and the mixture was stirred at rt for 30 min. H_2O was added to the mixture, which was extracted with CH_2Cl_2. The organic layer was washed with H_2O and brine, dried ($MgSO_4$), and concentrated in vacuo. Purification of the residue by column chromatography (1:3 EtOAc–hexane) gave 272 mg (quant.) of the acetate (3*S*,6*R*)-**2** as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.13 (s, 6H, –$SiCH_3$), 0.91 (s, 9H, –^{t}Bu), 2.08 (s, 3H, $COCH_3$), 3.82–3.85 (m, 2H, CH_2), 5.24 (m, 1H, –CH), 5.27 (dd, 1H, J=1.6, 1.3 Hz, –CH), 5.81–5.89 (m, 2H, –C*H*=C*H*); IR (neat) 1742 cm^{-1}; MS (FAB, +NaCl) m/z 295 $(M+Na)^+$; $[\alpha]_D^{20}=65.5$ (c 0.55, $CHCl_3$); anal. calcd for $C_{13}H_{24}O_4Si$: C, 57.32; H, 8.88. Found: C, 57.09; H, 8.77.

3.9. (3S,6S)-trans-6-Allyl-3,6-dihydro-2H-pyran-3-yl acetate; (3S,6S)-7

To a solution of (3*S*,6*R*)-**2** (236 mg, 0.867 mmol) and allyltrimethylsilane (225 mg, 1.73 mmol) in CH_2Cl_2 (4.0 mL) was added $BF_3{\cdot}OEt_2$ at −78°C, then the mixture was warmed up to −20°C over 15 min. After stirring at −20°C for 1 h, the mixture was poured into saturated $NaHCO_3$ and extracted with CH_2Cl_2. The organic layer was washed with brine, dried ($MgSO_4$), and concentrated in vacuo. Purification of the residue by column chromatography (1:8 EtOAc–hexane) gave 143 mg (91%) of (3*S*,6*S*)-**7** as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.07 (s, 3H, –$COCH_3$), 2.23–2.40 (m, 2H, –C*H*$_2$CH=CH$_2$), 3.54 (dd, 1H, J=11.2, 7.0 Hz, –CH_2), 4.12 (dd, 1H, J=11.2, 4.9 Hz, –CH_2), 4.18 (m, 1H, –CH), 5.11 (m, 2H, –CH=C*H*$_2$), 5.24 (m, 1H, –CH), 5.80 (dt, 1H, J=10.4, 6.9 Hz, –C*H*=C*H*), 5.85 (m, 1H, –C*H*=CH_2), 5.90 (dt, 1H, J=10.4, 1.4 Hz, –CH=C*H*); IR (neat) 1740, 1372, 1235 cm^{-1}; MS (APCI) m/z 183 $(M+H)^+$; $[\alpha]_D^{20}=179.7$ (c 1.76, $CHCl_3$) [lit.[6a] $[\alpha]_D^{20}=175$ (c 1.79, $CHCl_3$)]. The spectral data of (3*S*,6*S*)-**7** were in accordance with those reported in the literature.[6a]

Acknowledgements

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