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Short Communication

Chromatographic resolution of racemic α-halocarboxylic acids and O-substituted α-hydroxycarboxylic acids via diastereomeric N-acyloxazolidinones

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ABSTRACT

Diastereomeric pairs of N-acyloxazolidinones, derived from (4R,5S)-4-methyl-5-phenyl-2-oxazolidinone (as a chiral derivatizing agent) and racemic α-halocarboxylic acids or O-substituted α-hydroxycarboxylic acids, were separated chromatographically on a large preparative scale and showed appreciable degrees of NMR-shift difference. The origins of the chromatographic separability of these diastereomers are discussed.

INTRODUCTION

Optically active α-halocarboxylic acids and α-hydroxycarboxylic acids are important chiral building blocks in the synthesis of many biologically active substances. The enantiomeric forms of α-halocarboxylic acids and O-substituted α-hydroxycarboxylic acids are generally prepared via either classical resolution with alkaloids or enzymes [1–5] or enantioselective synthesis using a chiral auxiliary [6–13]. In this paper we report that chiral oxazolidinones can be used as efficient chiral derivatizing agents for the chromatographic resolution of α-halocarboxylic acids and O-substituted α-hydroxycarboxylic acids via diastereomeric N-acyloxazolidinones. It has already been reported that chiral oxazolidinones as chiral derivatizing agents can be used to resolve amines [14].

EXPERIMENTAL

Apparatus

Preparative liquid chromatography was performed using a column of Merck Kieselgel 60 (70–230 mesh). All melting points were determined on a Thomas Hoover capillary melting point apparatus and were uncorrected. ¹H NMR

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spectra were obtained on a Varian Gemini 300 spectrometer. All chemical shift values are reported on the δ scale with respect to internal tetramethylsilane. Microanalyses were determined with a Perkin-Elmer Model 240 DS elemental analyser. An Enraf-Nonius CAD-4 diffractometer with graphite-monochromated Mo Kα radiation ($\lambda = 0.71073$ Å) was used for the measurement of diffraction intensities. All calculations for X-ray structures were carried out using an MVAX-3900 computer.

Reagents

(4R,5S)- 4 -Methyl- 5 -phenyl- 2 -oxazolidinone was prepared as described in the literature [15,16]. 2-Bromopropionyl bromide, 2-chloropropionyl chloride, (±)-2-bromobutyryl bromide, (±)-2 bromohexanoyl bromide, 2-bromophenylacetic acid, DL-2-phenoxypropionic acid and (±)-2-bromo-3-methylbutyric acid were purchased from Aldrich and used as received.

N-2-Bromopropionyl-(4S,5R)-4-methyl-5-phenyl-2-oxazolidinone (2a)

To 48.13 g (271 mmol) of (4R,5S)-4-methyl-5-phenyl-2-oxazolidinone dissolved in 450 ml of dry tetrahydrofuran (THF), 108.5 ml of n-butyllithium (2.5 M THF solution) were added at $-10°C$. The solution obtained was added to 28.4 ml (271 mmol) of racemic 2-bromopropionyl bromide (in 150 ml of dry THF) at $-30°C$. After 30 min, the reaction mixture was poured into ammonium chloride solution. The aqueous mixture was extracted with ethyl acetate and dried with anhydrous sodium sulphate. The solvent was removed at reduced pressure and then the diastereomeric mixture was separated by column chromatography [silica gel (70–230 mesh, 60 Å), eluent n-hexane–ethyl acetate (7:1)].

First eluted: N-[(2S)-2-bromopropionyl]-(4R,5S)- 4 -methyl- 5 -phenyl- 2- oxazolidinone. M.p. 90°C. ^{1}H NMR (300 MHz, CDCl$_3$): δ 0.94 [d, J = 6.6 Hz, 3H, –NCH(CH$_3$)–], 1.86 [d, J = 6.7 Hz, 3H, CH$_3$CH(Br)–], 4.77 ["p" from qd, J = 6.7 Hz, 1H, –NCH(CH$_3$)CHO–], 5.76 [q, J = 6.7 Hz, 1H, CH$_3$CH(Br)–], 5.76 [d, J =

6.7 Hz, 1H, –NCH(CH$_3$)CHO–], 7.2–7.5 (m, 5H, C$_6$H$_5$–). Analysis: calculated for C$_{13}$H$_{14}$BrNO$_3$, C 50.0, H 4.5, N 4.5; found, C 50.1, H4.5, N 4.3%.

Second eluted: N-[(2R)-2-bromopropionyl]-(4R,5S)- 4 -methyl- 5 -phenyl- 2 -oxazolidinone. M.p. 98°C. ^{1}H NMR (300 MHz, CDCl$_3$): δ 0.91 [d, J = 6.6 Hz, 3H, –NCH(CH$_3$)–], 1.86 [d, J = 6.7 Hz, 3H, CH$_3$CH(Br)–], 4.84 ["p" from qd, J = 6.7 Hz, –NCH(CH$_3$)CHO–], 5.70 [q, J = 6.7 Hz, 1H, CH$_3$CH(Br)–], 5.73 [d, J = 6.7 Hz, 1H, –NCH(CH$_3$)CHO–], 7.2–7.5 (m, 5H, C$_6$H$_5$–). Analysis: calculated for C$_{13}$H$_{14}$BrNO$_3$, C 50.0, H 4.5, N 4.5; found, C 50.1, H 4.5, N 4.3%.

N-2-Chloropropionyl-(4R,5S)-4-methyl-5-phenyl-2-oxazolidinone (2b)

First eluted: N-[(2S)-2-chloropropionyl]-(4R,5S)- 4 -methyl- 5 -phenyl- 2 -oxazolidinone. M.p. 102°C. ^{1}H NMR (300 MHz, CDCl$_3$): δ 0.93 [d, J = 7.0 Hz, 3H, –NCH(CH$_3$)–], 1.72 [d, J = 6.6 Hz, 3H, CH$_3$CH(Cl)–], 4.78 ["p" from qd, J = 6.7 Hz, 1H, –NCH(CH$_3$)CHO–], 5.70 [q, J = 6.6 Hz, 1H, CH$_3$CH(Cl)–], 5.76 [d, J = 7 Hz, 1H, –NCH(CH$_3$)CHO–], 7.2–7.6 (m, 5H, C$_6$H$_5$–). Analysis: calculated for C$_{13}$H$_{14}$ClNO$_3$, C 58.33, H 5.27, N 5.23; found, C58.4, H5.21, N 5.00%.

Second eluted: N-[(2R)-2-chloropropionyl]-(4R,5S)- 4 -methyl- 5 -phenyl- 2 -oxazolidinone. M.p. 95°C. ^{1}H NMR (300 MHz, CDCl$_3$): δ 0.92 [d, J = 7.0 Hz, 3H, –NCH(CH$_3$)–], 1.72 [d, J = 6.7 Hz, 3H, CH$_3$CH(Cl)–], 4.81 ["p" from qd, J = 6.7 Hz, 1H, –NCH(CH$_3$)CHO–], 5.70 [q, J = 6.6 Hz, 1H, CH$_3$CH(Cl)–], 5.72 [d, J = 6.8 Hz, 1H, –NCH(CH$_3$)CHO–], 7.2–7.6 (m, 5H, C$_6$H$_5$–). Analysis: calculated for C$_{13}$H$_{14}$ClNO$_3$, C 58.33, H 5.27, N 5.23; found, C 58.4, H 5.23, N 5.07%.

N-2-Bromobutanoyl-(4R,5S)-4-methyl-5-phenyl-2-oxazolidinone (2c)

First eluted: N-[(2S)-2-bromobutanoyl]-(4R,5S)- 4 -methyl- 5 -phenyl- 2 -oxazolidinone. M.p. 69°C. ^{1}H NMR (300 MHz, CDCl$_3$): δ 0.94 [d, J = 6.6 Hz, 3H, –NCH(CH$_3$)–], 1.06 [t, J = 6.7 Hz, 3H, CH$_3$CH$_2$CH(Br)–], 2.11 [m, 2H, CH$_3$CH$_2$CH(Br)–], 4.81 ["p" from qd, J = 6.7

Hz, 1H, –NCH(CH$_3$)CHO–], 5.61 [t, J = 6.6 Hz, 1H, CH$_3$CH$_2$CH(Br)–], 5.77 [d, J = 6.7 Hz, 1H, –NCH(CH$_3$)CHO–], 7.2–7.5 (m, 5H, C$_6$H$_5$–). Analysis: calculated for C$_{14}$H$_{16}$BrNO$_3$, C 51.5, H 4.9, N 4.3; found, C 51.3, H 4.9, N 4.1%.

Second eluted: N-[(2R)-2-bromobutanoyl]-(4R,5S)- 4 -methyl- 5 -phenyl- 2 -oxazolidinone. M.p. 94°C. ¹H NMR (300 MHz, CDCl$_3$): δ 0.90 [d, J = 6.6 Hz, 3H, –NCH(CH$_3$)–], 1.06 [t, J = 6.7 Hz, 3H, CH$_3$CH$_2$CH(Br)–], 2.11 [m, 2H, CH$_3$CH$_2$CH(Br)–], 4.83 ["p" from qd, J = 6.7 Hz, 1H, –NCH(CH$_3$)CHO–], 5.54 [t, J = 6.6 Hz, 1H, CH$_3$CH$_2$CH(Br)–], 5.70 [d, J = 6.7 Hz, 1H, –NCH(CH$_3$)CHO–], 7.2–7.5 (m, 5H, C$_6$H$_5$–). Analysis: calculated for C$_{14}$H$_{16}$BrNO$_3$, C 51.5, H 4.9, N 4.3; found, C 51.3, H 5.0, N 4.3%.

N-2-Bromo-3-methylbutanoyl-(4R,5S)-4-methyl-5-phenyl-2-oxazolidinone (2d)

First eluted: N-[(2S)-2-bromo-3-methylbutanoyl]-(4R,5S)- 4 -methyl- 5 -phenyl- 2 -oxazolidinone. ¹H NMR (300 MHz, CDCl$_3$): δ 0.94 [d, J = 6.7 Hz, 3H, –NCH(CH$_3$)–] 1.05 [d, J = 6.6 Hz, 3H, (CH$_3$)$_2$CH–], 1.15 [d, J = 6.7 Hz, 3H, (CH$_3$)$_2$CH–], 2.35 [sym.m, 1H, (CH$_3$)$_2$CH–], 4.82 ["p" from qd, J = 6.7 Hz, 1H, –NCH(CH$_3$)CH(C$_6$H$_5$)–], 5.56 [d, J = 6.6 Hz, 1H, (CH$_3$)$_2$CHCH(Br)–], 5.75 [d, J = 6.8 Hz, 1H, –NCH(CH$_3$)CH(C$_6$H$_5$)–], 7.2–7.6 (m, 5H, –C$_6$H$_5$–].

Second eluted: N-[(2R)-2-bromo-3-methylbutanoyl]-(4R,5S)- 4 -methyl- 5 -phenyl- 2 -oxazolidinone. ¹H NMR (300 MHz, CDCl$_3$): δ 0.91 [d, J = 6.8 Hz, 3H, –NCH(CH$_3$)–] 1.06 [d, J = 6.6 Hz, 3H, (CH$_3$)$_2$CH–], 1.15 [d, J = 6.6 Hz, 3H, (CH$_3$)$_2$CH–], 2.37 [m, 1H (CH$_3$)$_2$CH–], 4.84 ["p" from qd, J = 6.8 Hz, 1H, –NCH(CH$_3$)CH(C$_6$H$_5$)–], 5.49 [d, J = 6.6 Hz, 1H, (CH$_3$)$_2$CHCH(Br)–], 5.71 [d, J = 6.7 Hz, 1H, –NCH(CH$_3$)CH(C$_6$H$_5$)–], 7.2–7.6 [m, 5H, C$_6$H$_5$–].

N-2-Bromohexanoyl-(4R,5S)-4-methyl-5-phenyl-2-oxazolidinone (2e)

First eluted: N-[(2S)-2-bromohexanoyl]-(4R,5S)- 4 -methyl- 5 -phenyl- 2 -oxazolidinone. M.p. 110°C. ¹H NMR (300 MHz, CDCl$_3$): δ 0.94 [br d, 6H, CH$_3$CH$_2$– and –NCH(CH$_3$)–], 1.3–1.6 (m, 4H, CH$_3$CH$_2$CH$_2$–), 1.9–2.2 [m, 2H, –CH$_2$CH(Br)–], 4.80 ["p" from qd, J = 6.7 Hz, 1H, –NCH(CH$_3$)CH(C$_6$H$_5$)–], 5.67 [t, J = 7.1 Hz, 1H, –CH$_2$CH(Br)–], 5.75 [d, J = 7.1 Hz, 1H, –NCH(CH$_3$)CH(C$_6$H$_5$)–], 7.2–7.6 (m, 5H, C$_6$H$_5$–). Analysis: calculated for C$_{16}$H$_{20}$BrNO$_3$, C 54.25, H 5.69, N 3.95; found, C 54.3, H 5.65, N 3.90%.

Second eluted: N-[(2R)-2-bromohexanoyl]-(4R,5S)- 4 -methyl- 5 -phenyl- 2 -oxazolidinone. M.p. 89°C. ¹H NMR (300 MHz, CDCl$_3$): δ 0.91 [br d, 6H, CH$_3$CH$_2$– and –NCH(CH$_3$)–], 1.2–1.6 (m, 4H, CH$_3$CH$_2$CH$_2$–), 1.9–2.2 [m, 2H, –CH$_2$CH(Br)–], 4.80 ["p" from qd, J = 6.7 Hz, 1H, –NCH(CH$_3$)CH(C$_6$H$_5$)–], 5.67 [t, J = 7.1 Hz, 1H, –CH$_2$CH(Br)–], 5.75 [d, J = 7.1 Hz, 1H, –NCH(CH$_3$)CH(C$_6$H$_5$)–], 7.2–7.6 (m, 5H, C$_6$H$_5$–). Analysis: calculated for C$_{16}$H$_{20}$BrNO$_3$, C 54.25, H 5.69, N 3.95; found, C 54.3, H 5.65, N 3.90%.

N-2-Bromophenylacetyl-(4R,5S)-4-methyl-5-phenyl-2-oxazolidinone (2f)

First eluted: N-[(2S)-bromophenylacetyl-(4R,5S)-4-methyl-5-phenyl-2-oxazolidinone. ¹H NMR (300 MHz, CDCl$_3$): δ 0.83 [d, J = 7.4 Hz, 3H, –NCH(CH$_3$)–], 4.87 ["p" from qd, J = 6.8 Hz, 1H, –NCH(CH$_3$)CH(C$_6$H$_5$)–], 5.76 [d, J = 7.0 Hz, 1H, –NCH(CH$_3$)CH(C$_6$H$_5$)–], 6.88 [s, 1H, C$_6$H$_5$CH(Br)–], 7.2–7.7 [m, 10H, C$_6$H$_5$CH(Br) and –NCH(CH$_3$)CH(C$_6$H$_5$)–].

Second eluted: N-[(2R)-bromophenylacetyl-(4R,5S)-4-methyl-5-phenyl-2-oxazolidinone. ¹H NMR (300 MHz, CDCl$_3$): δ 0.79 [d, J = 7.2 Hz, 3H, –NCH(CH$_3$)–], 4.87 ["p" from qd, J = 6.6 Hz, 1H, –NCH(CH$_3$)CH(C$_6$H$_5$)–], 5.74 [d, J = 6.8 Hz, 1H, –NCH(CH$_3$)CH(C$_6$H$_5$)–], 6.81 [s, 1H, C$_6$H$_5$CH(Br)–], 7.2–7.7 [m, 10H, C$_6$H$_5$CH(Br) and –NCH(CH$_3$)CH(C$_6$H$_5$)–].

N-2-Phenoxypropionyl-(4R,5S)-4-methyl-5-phenyl-2-oxazolidinone (2g)

First eluted: N-[(2S)-2-phenoxypropionyl]-(4R,5S)-4-methyl-5-phenyl-2-oxazolidinone. ¹H NMR (300 MHz, CDCl$_3$): δ 0.91 [d, J = 6.6 Hz, 3H, –NCH(CH$_3$)–], 1.67 [d, J = 6.6 Hz, 3H,
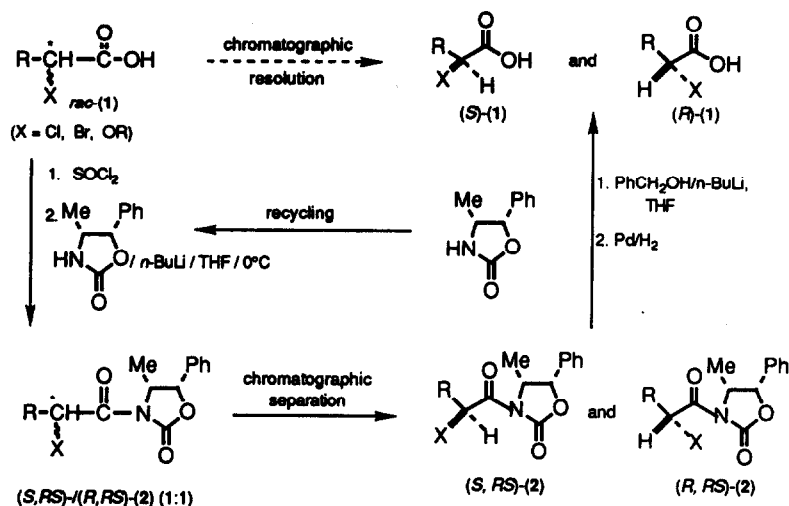
Fig. 1. Chromatographic resolution of α-halo acids and O-substituted α-hydroxy acids.

$CH_3CH(OC_6H_5)$–], 4.80 ["p" from qd, $J = 6.6$ Hz, 1H, $-NCH(CH_3)CH(C_6H_5)$–], 5.77 [d, $J = 6.6$ Hz, 1H, $-NCH(CH_3)CH(C_6H_5)$–], 6.03 [q, $J = 6.6$ Hz, 1H, $CH_3CH(OC_6H_5)$–], 6.8–7.6 [m, 10H, $-OC_6H_5$ and $-NCH(CH_3)CH(C_6H_5)$–].

Second eluted: N-[(2R)-2-phenoxypropionyl]-(4R,5S)-4-methyl-5-phenyl-2-oxazolidinone. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.91 [d, $J = 6.6$ Hz, 3H, $-NCH(CH_3)$–], 1.67 [d, $J = 6.6$ Hz, 3H, $CH_3CH(OC_6H_5)$–], 4.83 ["p" from qd, $J = 6.7$
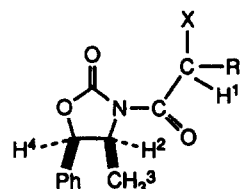
TABLE I

NMR AND CHROMATOGRAPHIC PROPERTIES OF DIASTEREOMERIC N-ACYLOXAZOLIDINONES

Compound	R	X	α^a	Chemical shift[b] (ppm)								Configuration of acid[d]
				δ_1	$\Delta\delta_1{}^c$	δ_2	$\Delta\delta_2{}^c$	δ_3	$\Delta\delta_3{}^c$	δ_4	$\Delta\delta_4{}^c$	
2a	CH_3	Br	2.60	5.75	0.05	4.77	−0.07	0.94	0.03	5.76	0.03	S
2b	CH_3	Cl	2.24	5.76	0.04	4.78	−0.03	0.93	0.01	5.70	0	S
2c	Et	Br	1.78	5.77	0.07	4.81	−0.02	0.94	0.04	5.61	0.07	S
2d	i-Pr	Br	1.64	5.75	0.04	4.82	−0.02	0.94	0.03	5.56	0.07	S
2e	n-Bu	Br	1.40	5.75	0.05	4.80	−0.04	0.94	0.03	5.67	0.05	S
2f	Ph	Br	1.13	6.88	0.07	4.87	0	0.83	0.04	5.76	0.02	S
2g	CH_3	OPh	1.85	6.03	0.07	4.78	−0.03	0.91	0	5.77	0.01	S

[a] These non-optimized separations were achieved by normal preparative liquid chromatography using silica gel (70–230 mesh, 60 Å) as stationary phase and eluting with ethyl acetate–hexane (1:7).
[b] Chemical shifts (δ) are given for high R_f diastereomer in parts per million, downfield of Me_4Si.
[c] $\Delta\delta = \delta_{high\ R_f} - \delta_{low\ R_f}$.
[d] Configuration is that of the high R_f diastereomer.

Hz, 1H, $-NCH(CH_3)CH(C_6H_5)-$], 5.76 [d, $J = $ 6.8 Hz, 1H, $-NCH(CH_3)CH(C_6H_5)-$], 5.96 [q, $J = 6.7$ Hz, 1H, $CH_3CH(OC_6H_5)-$], 6.8–7.6 [m, 10H, $-OC_6H_5$ and $-NCH(CH_3)CH(C_6H_5)-$].

RESULTS AND DISCUSSION

As depicted in Fig. 1, the diastereomeric N-acyloxazolidinones **2** were prepared in quantitative yield by lithiation of (4R,5S)-4-methyl-5-phenyl-2-oxazolidinone (n-butyllithium, 2.5 M THF) and subsequent reaction with racemic α-halocarboxylic acid chlorides or O-substituted α-hydroxycarboxylic acid chlorides. Each diastereomer was easily separated chromatographically on a large scale. As is shown in Table I, in the case of the typical examples **2a**, **2b** and **2c**, chromatographic separation factors of $\alpha = 1.8$–2.6 are achieved under preparative conditions. The pure diastereomer were cleaved by esterification and subsequent hydrolysis by the well known procedure to yield enantiomerically pure (R)- and (S)-acids [17]. Further, the consistent elution orders (the [S, (R,S)]-diastereomer always elutes first) can be used to indicate the absolute configuration of acids.

The chemical shift difference ($\Delta\delta$) of the diastereomer is also appreciable (Table I). This permits the NMR determination of enantiomeric purity and absolute configuration for α-halocarboxylic acids and O-substituted α-hydroxycarboxylic acids. Especially the single decoupling operation can make the integration easy.

One plausible explanation for this high degree of chromatographic separability and NMR shift difference could be associated with the conformational rigidity of diastereomers **2**. As can be seen from the X-ray structure of the second-eluted diastereomer of **2a**, (R,RS)-**2a** (Fig. 2). the eight atoms C(1), C(3), O(1), N, C(4), C(6), O(2) and O(3) form a plane (defined by the equation $0.8715x - 0.4305y - 0.2347z = 0.5589$), since none of these atoms is displaced by more than 0.134(7) Å. Further, the intramolecular contact distances of Br–O(1) and Br–O(2) are 3.476(6) and 3.420(6) Å, respectively, which are very close to the sums of their Van der Waals radii (sum of Van der Waals
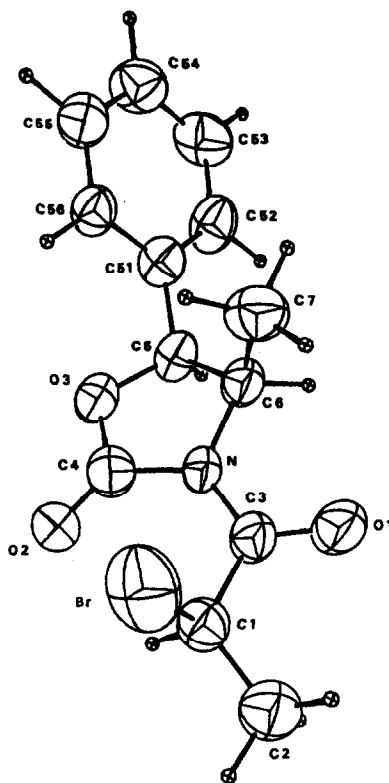

Fig. 2. X-ray structure of (R, RS)-**2a**.

radius of Br and O = 3.3–3.5 Å). These facts resulted from the steric hindrance between Br and O(2), and then the C(1)–C(3) single bond cannot rotate easily. Hence this diastereomer is conformationally rigid. This conformational rigidity causes a difference in polarity and confers a high degree of chromatographic separability and NMR shift difference on diastereomers. In Table II, relevant intramolecular contact distances are given.

In conclusion, we found that chiral oxazolidinones are valuable derivatizing agents for the chromatographic resolution of α-halocarbox-

TABLE II

INTRAMOLECULAR CONTACT DISTANCES (Å) FOR (R, RS)-**2a**

Br–O(1)	3.476(6)	Br–O(2)	3.420(6)
Br–N	3.370(5)	Br–C(4)	3.638(8)
C(2)–O(1)	2.79(1)	C(2)–N	3.76(1)
C(7)–O(1)	3.20(1)	C(1)–O(2)	2.894(9)

ylic acids and O-substituted α-hydroxycarboxylic acids.

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