A New General and Facile Method for the Synthesis of 4-Alkyl-1,3-oxazoline-4-carboxylic Acids from *N*-Acyl-2-alkylserines

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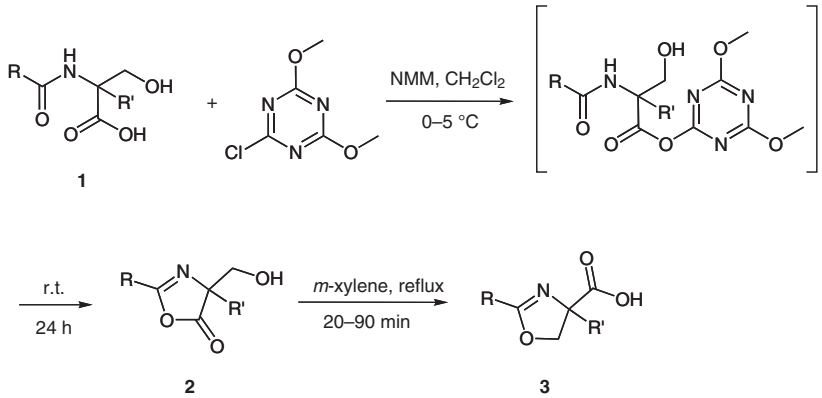
Abstract: A new synthesis of 4-alkyl-1,3-oxazoline-4-carboxylic acids involves the thermal rearrangement of 4-alkyl-4-hydroxymethyl-1,3-oxazolin-5-ones prepared from *N*-acyl-2-alkylserines or N-protected peptides with a C-terminal 2-alkylserine residue. The rearrangement is fast and affords HPLC pure title compounds in 68–96% yield both from racemic and enantiomerically pure *N*-acyl-2-alkyl serines as well as from respective peptides.

Key words: 2-alkylserines, heterocycles, rearrangement

Derivatives of oxazole and thiazole carboxylic acids and their dihydro analogues are substructures of numerous natural products.[1] Many of them are found in pharmaceutically interesting antibiotics[2] and others.[3,4] The biogenesis of oxazole heterocycles is believed to proceed from amino acid or peptide substrates. Cyclodehydration involving serine or threonine side chains creates dihydroheterocycles – oxazoline and methyloxazoline, respectively – which subsequently can undergo reduction to an oxazolidine or oxidation to an oxazole. All three oxidation states of these heterocycles were found in biologically active compounds. Heterocyclization alters the peptide backbone, connectivity, and electronic distribution, and affords new elements for highly specific recognition and interactions with targets such as DNA, RNA, or proteins. From that point of view 4-alkyl-1,3-oxazoline-4-carboxylic acids derived from 2-alkylserines deserve special attention[5] because of severely reduced conformational flexibility.[6] 2-Alkylserines themselves are the object of extensive studies[7] as substitutes of the serine residue in the active site of peptides, strongly influencing their activity.[8] In most of the cases, esters of 1,3-oxazoline-4-carboxylic acids and their 4-substituted analogues were prepared by multistep procedures by modification of appropriate serine derivatives,[9] application of Burgess reagent,[10] or others.[11] Herein we describe a general, simple, and efficient method of preparation of 4-alkyl-1,3-oxazoline-4-carboxylic acids **3** based on the new rearrangement[12] of 4-alkyl-4-hydroxymethyl-1,3-oxazolin-5-ones **2** readily accessible by cyclodehydration of *N*-acyl-2-alkylserines **1** (Scheme 1).

The *N*-acyl-2-alkylserines **1** when treated at 0–5 °C with 2-chloro-4,6-dimethoxy-1,3,5-triazine (CDMT) in the presence of *N*-methylmorpholine (NMM) were converted into 'superactive esters', which at room temperature easily underwent cyclization to 4-alkyl-4-hydroxymethyl-1,3-oxazolin-5-ones **2** in almost quantitative yields (Table 1). This protocol was advantageous because any side products were easily removed by simple extractive work-up, affording crude **2** which was sufficiently pure (95–98% by HPLC) for the next synthetic step.

1,3-Oxazolin-5-ones **2a–e** subsequently rearranged within 20–90 minutes in boiling *m*-xylene into 4-alkyl-1,3-oxazoline-4-carboxylic acids **3a–e** in excellent yields. We have found that the rearrangement[12] of **2a** proceeded also



Scheme 1 Synthesis of 4-alkyl-1,3-oxazoline-4-carboxylic acids from *N*-acyl-2-alkylserines

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Table 1 Synthesis of 4-Alkyl-1,3-oxazoline-4-carboxylic Acids **3** from *N*-Acyl-2-alkylserines **1a–e** and Peptides **1f,g** via 4-Alkyl-4-hydroxymethyl-1,3-oxazolin-5-ones **2a–g**

1	RCO	R′	2 Yield (%)[a]	3 Yield (%)[a]
1a	benzoyl	Me	**2a** 90	**3a** 70
(*S*)-**1a**	benzoyl	Me	(*S*)-**2a** 92	(*S*)-**3a** 72
1b	benzoyl	Et	**2b** 90	**3b** 80
1c	benzoyl	*i*-Pr	**2c** 87	**3c** 91
1d	benzoyl	*i*-Bu	**2d** 98	**3d** 68
1e	benzoyl	Bn	**2e** 99	**3e** 96
(*S*)-**1e**	benzoyl	Bn	(*S*)-**2e** 90	(*S*)-**3e** 90
(*R*)-**1e**	benzoyl	Bn	(*R*)-**2e** 91	(*R*)-**3e** 88
1f	Z-Aib[b]	Me	**2f** 99	**3f** 92
1g	Z-Ach[c]	Me	**2g** 98	**3g** 94

[a] Isolated yields.
[b] Z-Aib: *N*-benzyloxycarbonylaminoisobutyryl.
[c] Z-Ach: *N*-benzyloxycarbonylaminocyclohexanoyl.

in boiling toluene or benzene, but in those solvents prolonged reaction times were required. 1,3-Oxazolin-5-ones **2f,g** derived from N-protected dipeptides **1f,g** containing a 2-alkylserine residue in the C-terminal position rearranged noticeably less readily although appropriate **3f,g** were also isolated in high yield. Determination of an optical purity of **3a,e** by HPLC on chiral stationary phase confirmed that rearrangement of optically active **1a,e** proceeded without loss of enantiomeric homogeneity.

In conclusion, the availability of 4-substituted 1,3-oxazoline-4-carboxylic acids provides convenient access for their application as sterically hindered building blocks with reduced conformational flexibility for a construction of new peptidomimetics, polyazole antibiotics, or DNA bonding oligopeptides. Moreover, one can expect that the conformation adopted by a peptide that incorporates an oxazoline ring will offer a new structural motif, resembling, but not identical to, proline or oxoproline analogues.[13] Experiments on the synthesis of peptides from 4-alkyl-1,3-oxazoline-4-carboxylic acids are in progress.

N-Methylmorpholine (reagent grade) was stored over KOH, CH_2Cl_2 was dried over $CaCl_2$. Racemic *N*-benzoyl-2-alkylserines[14] and 2-chloro-4,6-dimethoxy-1,3,5-triazine[15] (CDMT) were prepared according to procedure described previously. Enantiomerically pure *N*-benzoyl-2-methyl- and *N*-benzoyl-2-benzylserines were obtained by enzymatic resolution of racemates.[16] All other reagents from commercial sources were used as received. IR spectra were recorded on a Specord-IR 71 spectrometer; solids were recorded as KBr discs, unless otherwise stated. ^{1}H NMR (250 MHz) and ^{13}C NMR (62.5 MHz) spectra were taken on a Bruker DPX 250 spectrometer in $CDCl_3$ with tetramethylsilane as an internal standard. Analytical high-performance liquid chromatography was done on Dionex ASI 100 chromatograph consisting of oven, autosampler and UV-diode-array detector. Chiral stationary phase (*S*,*S*)-Whelk-O1 column was used with a mixture of hexane–propan-2-ol (8:2) at 2 mL/min as mobile phase. Specific rotations were measured on Rudolph Research Autopol IV polarimeter in 1 dm tube at the sodium D line. Concentrations are given in g/100 mL. Melting points were determined in open capillary tubes and are uncorrected.

4-Alkyl-4-hydroxymethyl-1,3-oxazolin-5-ones 2; General Procedure

To a stirred solution of CDMT (0.352 g, 2 mmol) in CH_2Cl_2 (10 mL), was added *N*-methylmorpholine (0.22 mL, 2 mmol) at 0–5 °C, followed by addition of the *N*-acyl-2-alkylserine **1** (2 mmol). The mixture was stirred for 24 h at r.t., then diluted with CH_2Cl_2 (30 mL), successively washed with distilled H_2O (20 mL), aq 1 M $NaHSO_4$ (3 × 10 mL), aq 1 M $NaHCO_3$ (3 × 10 mL), H_2O (1 × 20 mL), and dried ($MgSO_4$). The solvent was evaporated under reduced pressure and the residue dried in a desiccator over KOH and P_2O_5. Product was of 95–98% purity according to HPLC analysis and was directly used in the next step.

4-Hydroxymethyl-4-methyl-2-phenyl-1,3-oxazolin-5-one (*rac*-2a)

White solid; yield: 90%; mp 125–127 °C.

^{1}H NMR: δ = 1.47 (s, 3 H), 3.88 (d, *J* = 11.3 Hz, 1 H), 3.95 (d, *J* = 11.3 Hz, 1 H), 7.45–7.58 (m, 3 H), 7.97–8.00 (m, 2 H).

^{13}C NMR: δ = 18.9, 66.5, 77.5, 127.9, 128.4, 128.7, 133.5, 161.9, 173.9.

(*S*)-4-Hydroxymethyl-4-methyl-2-phenyl-1,3-oxazolin-5-one [(*S*)-2a]

White solid; yield: 92%; mp 116–118 °C; $[\alpha]_D^{24}$ –1.8 (*c* 2.5, $CHCl_3$).

^{1}H NMR and ^{13}C NMR spectra were identical to those of *rac*-**2a**.

4-Ethyl-4-hydroxymethyl-2-phenyl-1,3-oxazolin-5-one (*rac*-2b)

Oil; yield: 90%.

^{1}H NMR: δ = 0.88 (t, *J* = 7.4 Hz, 3 H), 1.9 (dq, *J* = 7.4 Hz, 2 H), 3.99 (d, *J* = 11.3 Hz, 1 H), 4.05 (d, *J* = 11.3 Hz, 1 H), 7.44–7.59 (m, 3 H), 7.98–8.02 (m, 2 H).

^{13}C NMR: δ = 7.8, 26.2, 66.1, 77.5, 125.4, 128.0, 128.8, 132.9, 162.1, 178.8.

4-Hydroxymethyl-4-isopropyl-2-phenyl-1,3-oxazolin-5-one (*rac*-2c)

Oil; yield: 87%.

^{1}H NMR: δ = 0.92 (d, *J* = 6.8 Hz, 3 H), 1.04 (d, *J* = 6.8 Hz, 3 H), 2.23 (sept, *J* = 6.8 Hz, 1 H), 3.98 (d, *J* = 12.3 Hz, 1 H), 4.01 (d, *J* = 12.3 Hz, 1 H), 7.44–7.57 (m, 3 H), 7.97–8.01 (m, 2 H).

^{13}C NMR: δ = 15.4, 15.5, 29.9, 63.1, 77.2, 123.6, 126.2, 127.4, 131.0, 160.3, 177.0.

4-Hydroxymethyl-4-isobutyl-2-phenyl-1,3-oxazolin-5-one (*rac*-2d)

Oil; yield: 98%.

^{1}H NMR: δ = 0.84 (d, *J* = 6.5 Hz, 3 H), 0.89 (d, *J* = 6.5 Hz, 3 H), 1.65–1.88 (m, 3 H), 3.85 (d, *J* = 11.3 Hz, 1 H), 3.90 (d, *J* = 11.3 Hz, 1 H), 7.43–7.57 (m, 3 H), 7.95–7.99 (m, 2 H).

^{13}C NMR: δ = 22.9, 23.9, 25.5, 42.4, 67.1, 76.0, 125.4, 128.0, 128.8, 132.9, 161.7, 179.4.

4-Benzyl-4-hydroxymethyl-2-phenyl-1,3-oxazolin-5-one (*rac*-2e)

White solid; yield: 99%; mp 121–122 °C.

^{1}H NMR: δ = 3.08 (d, *J* = 13.5 Hz, 1 H), 3.15 (d, *J* = 13.5 Hz, 1 H), 3.95 (d, *J* = 11.4 Hz, 1 H), 4.06 (d, *J* = 11.4 Hz, 1 H), 7.18 (br s, 5 H), 7.25–7.48 (m, 3 H), 7.73–7.77 (m, 2 H).

^{13}C NMR: δ = 39.1, 66.0, 126.8, 127.2, 127.7, 128.1, 128.5, 129.6, 129.9, 132.7, 162.1, 177.6.

(*S*)-4-Benzyl-4-hydroxymethyl-2-phenyl-1,3-oxazolin-5-one [(*S*)-2e]
White solid; yield: 90%; mp 103–104 °C; $[\alpha]_D^{24}$ –135.5 (*c* 2.5, $CHCl_3$).

^{1}H NMR and ^{13}C NMR spectra were identical to those of *rac*-**2e**.

(*R*)-4-Benzyl-4-hydroxymethyl-2-phenyl-1,3-oxazolin-5-one [(*R*)-2e]
White solid; yield: 91%; mp 104–105 °C; $[\alpha]_D^{24}$ +142.0 (*c* 2.5, $CHCl_3$).

^{1}H NMR and ^{13}C NMR spectra were identical to those of *rac*-**2e**.

2-(1-Benzyloxycarbonylamino-1-methylethyl)-4-hydroxymethyl-4-methyl-1,3-oxazolin-5-one (*rac*-2f)
White solid; yield: 99%; mp 130–131 °C.

IR (CCl_4): 3472, 3320, 1820, 1684, 1536, 1288, 1096, 1032, 796 cm^{-1}.

^{1}H NMR: δ = 1.35 (s, 3 H), 1.59 (s, 3 H), 1.65 (s, 3 H), 3.73 (m, 2 H), 5.02 (d, *J* = 12.5 Hz, 1 H), 5.09 (d, *J* = 12.5 Hz, 1 H), 5.20 (br s, 1 H), 7.35 (br s, 5 H).

^{13}C NMR: δ = 17.9, 25.0, 25.1, 52.4, 67.0, 67.8, 72.1, 128.1, 128.2, 128.5, 135.8, 155.2, 167.0, 179.2.

2-(1-Benzyloxycarbonylamino-1-cyclohexyl)-4-hydroxymethyl-4-methyl-1,3-oxazolin-5-one (*rac*-2g)
Oil; yield: 98%.

IR (film): 3336, 3032, 2936, 2864 1820, 1788, 1716, 1528, 1464, 1448, 1368, 1256, 1008, 916, 732 cm^{-1}.

^{1}H NMR: δ = 1.33 (s, 3 H), 1.18–1.99 (m, 10 H), 3.99 (d, *J* = 8.8 Hz, 1 H), 4.05 (d, *J* = 8.8 Hz, 1 H), 5.02 (d, *J* = 12 Hz, 1 H), 5.08 (d, *J* = 12 Hz, 1 H), 5.43 (br s, 1 H), 7.32 (br s, 5 H).

^{13}C NMR: δ = 17.9, 20.9, 24.8, 32.1, 32.4, 54.8, 66.9, 67.7, 71.9, 127.9, 128.1, 128.4, 135.8, 155.2, 166.6, 179.3.

4-Alkyl-1,3-oxazoline-4-carboxylic Acids 3; General Procedure
The appropriate 4-alkyl-4-hydroxymethyl-2-phenyl-1,3-oxazolin-5-one **2** (2 mmol) was dissolved in *m*-xylene (15 mL) and refluxed. HPLC analysis after 20–90 min showed complete conversion of starting material. The solvent was evaporated and the oily residue was treated with hexane under sonication. The precipitated solid was filtered, washed with hexane, and dried in a desiccator. Purity according to HPLC analysis was >99%.

4-Methyl-2-phenyl-1,3-oxazoline-4-carboxylic Acid (*rac*-3a)
White solid; yield: 70%; mp 115 °C (Lit.[9c] mp 130–132 °C).

HPLC: t_R (*S*) = 21.2 min (50%), t_R (*R*) = 22.4 min (50%).

IR (KBr): 3424, 3208, 2992, 1724, 1636, 1576, 1496, 1452, 1276 cm^{-1}.

^{1}H NMR: δ = 1.66 (s, 3 H), 4.28 (d, *J* = 9 Hz, 1 H), 4.85 (d, *J* = 9 Hz, 1 H), 7.40–7.56 (m, 3 H), 7.95–7.98 (m, 2 H).

^{13}C NMR: δ = 24.9, 73.6, 76.5, 126.0, 128.4, 128.7, 132.3, 165.8, 175.7.

Anal. Calcd for $C_{11}H_{11}NO_3 \cdot 0.25H_2O$: C, 63.00; H, 5.53; N, 6.68. Found: C, 62.69; H, 5.34; N, 6.96.

(*S*)-4-Methyl-2-phenyl-1,3-oxazoline-4-carboxylic Acid [(*S*)-3a]
White solid; yield: 72%; mp 111 °C; $[\alpha]_D^{24}$ +3.9 (*c* 5.0, MeOH).

HPLC: t_R (*S*) = 21.2 min (100%).

^{1}H NMR and ^{13}C NMR spectra were identical with those of *rac*-**3a**.

4-Ethyl-2-phenyl-1,3-oxazoline-4-carboxylic Acid (*rac*-3b)
White solid; yield: 80%; mp 110–111 °C.

HPLC: t_{R1} = 22.8 min (50%), t_{R2} = 26.7 min (50%).

IR (KBr): 3424, 3208, 2976, 2928, 1728, 1632, 1496, 1472, 1448, 1256 cm^{-1}.

^{1}H NMR: δ = 1.00 (t, *J* = 7.4, 3 H), 2.00 (dq, *J* = 7.1, 7.4, 2 H), 4.36 (d, *J* = 9 Hz, 1 H), 4.76 (d, *J* = 9 Hz, 1 H), 7.41–7.58 (m, 3 H), 7.96–7.99 (m, 2 H).

^{13}C NMR: δ = 7.8, 31.0, 73.9, 77.9, 126.0, 128.4, 128.7, 132.3, 165.9, 175.2.

Anal. Calcd for $C_{12}H_{13}NO_3 \cdot 0.5H_2O$: C, 63.15; H, 6.18; N, 6.14. Found: C, 63.30; H, 6.02; N, 6.24.

4-Isopropyl-2-phenyl-1,3-oxazoline-4-carboxylic Acid (*rac*-3c)
White solid; yield: 91%; mp 155–157 °C.

IR (KBr): 2968, 1728, 1640, 1480, 1448, 1360, 1292 cm^{-1}.

^{1}H NMR: δ = 0.81 (d, *J* = 6.8 Hz, 3 H), 0.86 (d, *J* = 6.8 Hz, 3 H), 2.25 (sept, *J* = 6.8 Hz, 1 H),), 4.26 (d, *J* = 9.1 Hz, 1 H), 4.65 (d, *J* = 9.1 Hz, 1 H), 7.32–7.47 (m, 3 H), 7.84–7.87 (m, 2 H).

^{13}C NMR (DMSO-d_6): δ = 16.7, 16.9, 33.1, 70.7, 82.3, 127.6, 127.8, 128.5, 131.2, 160.9, 174.2.

Anal. Calcd for $C_{11}H_{11}NO_3 \cdot 0.25H_2O$: C, 63.00; H, 5.53; N, 6.68. Found: C, 62.69; H, 5.34; N, 6.96.

4-Isobutyl-2-phenyl-1,3-oxazoline-4-carboxylic Acid (*rac*-3d)
White solid; yield: 68%; mp 81–82 °C.

IR (KBr): 3424, 3184, 2960, 1720, 1628, 1496, 1488, 1448, 1228 cm^{-1}.

^{1}H NMR: δ = 0.95 (d, *J* = 6.3 Hz, 3 H), 1.00 (d, *J* = 6.3 Hz, 3 H), 1.80–1.92 (m, 3 H), 4.35 (d, *J* = 9.2 Hz, 1 H), 4.83 (d, *J* = 9.2 Hz, 1 H), 7.40–7.54 (m, 3 H), 7.95–7.99 (m, 2 H).

^{13}C NMR: δ = 23.3, 23.9, 24.8, 47.0, 75.2, 76.5, 126.2, 128.4, 128.7, 132.3, 165.6, 175.5.

Anal. Calcd for $C_{11}H_{11}NO_3 \cdot 0.25H_2O$: C, 63.00; H, 5.53; N, 6.68. Found: C, 62.69; H, 5.34; N, 6.96.

4-Benzyl-2-phenyl-1,3-oxazoline-4-carboxylic Acid (*rac*-3e)
White solid; yield: 96%; mp 126–127 °C.

HPLC: t_R (*S*) = 16.1 min (50%), t_R (*R*) = 26.2 min (50%).

IR (KBr): 3472, 3160, 1724, 1628, 1576, 1496, 1448, 1272 cm^{-1}.

^{1}H NMR: δ = 3.18 (d, *J* = 13.6 Hz, 1 H), 3.35 (d, *J* = 13.6 Hz, 1 H), 4.46 (d, *J* = 9.3 Hz, 1 H), 4.76 (d, *J* = 9.3 Hz, 1 H), 7.22–7.27 (m, 5 H), 7.38–7.53 (m, 3 H), 7.90–7.94 (m, 2 H).

^{13}C NMR (acetone-d_6): δ = 43.2, 73.5, 79.0, 127.5, 128.1, 128.8, 129.1, 129.2, 131.4, 132.5, 136.6, 165.3, 173.9.

Anal. Calcd for $C_{17}H_{15}NO_3 \cdot 0.33H_2O$: C, 71.07; H, 5.50; N, 4.87. Found: C, 70.86; H, 5.16; N, 5.36.

(*S*)-4-Benzyl-2-phenyl-1,3-oxazoline-4-carboxylic Acid [(*S*)-3e]
White solid; yield: 90%; mp 120–121 °C; $[\alpha]_D^{25}$ +59.5 (*c* 2.5, MeOH).

HPLC: t_R (*S*) = 16.1 min (100%).

^{1}H NMR and ^{13}C NMR spectra were identical to those of *rac*-**3e**.

(*R*)-4-Benzyl-2-phenyl-1,3-oxazoline-4-carboxylic Acid [(*R*)-3e]
White solid; yield: 88%; mp 123–124 °C; $[\alpha]_D^{25}$ –67.0 (*c* 2.5, MeOH).

HPLC: t_R (*R*) = 26.2 min (100%).

^{1}H NMR and ^{13}C NMR spectra were identical to those of *rac*-**3e**.

2-(1-Benzyloxycarbonylamino-1-methylethyl)-4-methyl-1,3-oxazoline-4-carboxylic Acid (*rac*-3f)
White solid; yield: 92%; mp 102–103 °C.

IR (KBr): 3472, 3320, 1820, 1684, 1536, 1288, 1196, 1032, 796 cm^{-1}.

^{1}H NMR (DMSO-d_6): δ = 1.24 (s, 3 H), 1.33 (s, 3 H), 1.39 (s, 3 H), 4.09 (d, *J* = 11.3 Hz, 1 H), 4.27 (d, *J* = 11.3 Hz, 1 H), 4.99 (m, 2 H), 7.34 (br s, 5 H), 7.72 (br s, 2 H).

^{13}C NMR (DMSO-d_6): δ = 19.6, 24.9, 25.1, 55.9, 59.0, 65.5, 67.7, 127.7, 127.9, 128.3, 136.8, 155.5, 169.7, 173.8.

FAB-MS: *m*/*z* = 321 [(M + H)$^+$], 339 [(M + H + H_2O)$^+$].

2-(1-Benzyloxycarbonylamino-1-cyclohexyl)-4-methyl-1,3-oxazoline-4-carboxylic Acid *rac*-(3g)
White solid; yield: 94%; mp 134–136 °C.

IR (CCl_4): 3344, 2936, 2856, 1716, 1600, 1528, 1448, 1264, 784 cm^{-1}.

^{1}H NMR (DMSO-d_6): δ = 1.18 (s, 3 H), 1.10–1.93 (m, 10 H), 4.07 (d, *J* = 11.5 Hz, 1 H), 4.24 (d, *J* = 11.5 Hz, 1 H), 5.00 (m, 2 H), 7.36 (m, 5 H), 7.45 (br s, 2 H).

^{13}C NMR (DMSO-d_6): δ = 19.7, 20.8, 24.7, 31.8, 55.1, 58.9, 65.5, 67.6, 127.7, 127.9, 128.6, 136.8, 155.8, 169.6, 173.9.

FAB-MS: *m*/*z* = 361 [(M + H)$^+$], 379 [(M + H + H_2O)$^+$].

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