Highly Diastereoselective Total Syntheses of (+)-7-Epigoniodiol, (−)-8-Epigoniodiol, and (+)-9-Deoxygoniopypyrone

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An expedient concise total synthesis of (+)-7-epigoniodiol, (−)-8-epigoniodiol, and (+)-9-deoxygoniopypyrone is accomplished. The key transformations include a catalytic hydroxylation and base-mediated *N*-(acetyl)oxazolidinone addition reactions, which could set the consecutive OH motif that is either *syn,syn* or *syn,anti* with high diastereoselectivity. Moreover, this approach envisioned to facilitate the synthesis of other representatives of the family with structural and stereochemical variation.

Introduction. – Bioactivity-guided studies on the constituents of the Asian trees of the genus *Goniothalamus* led to the isolation of a number of therapeutic agents which exhibited significant cytotoxicities against several solid tumor lines in addition to antifungal, antibiotic properties [1]. The common sub-structural units found in these bioactive compounds are depicted in *Fig. 1* [2].

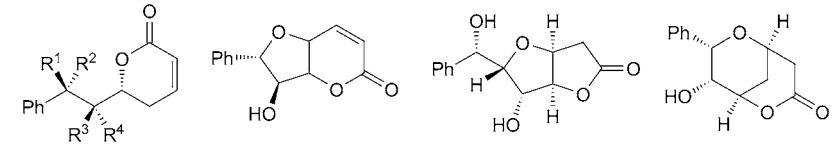


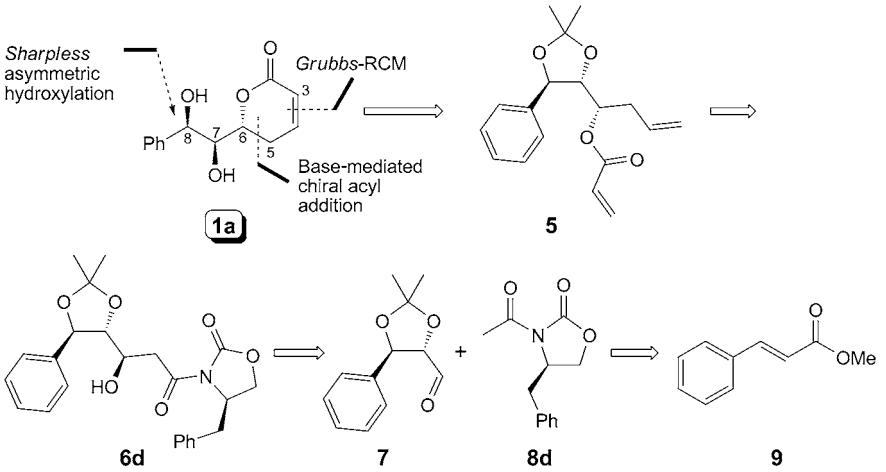
Fig. 1. *Bioactive 6-(1,2-dihydroxy-2-phenylethyl)pyran-2-one, furano-2-pyrone, furo[3,2-*b*]furan-2-one, and methano-1,5-dioxocan-2-one compounds*

Among them, the most exploited natural products were (2-phenylethyl)pyran-2-ones owing to their selective and remarkable cytotoxicities against human lung carcinoma cell lines A-549 (ED_{50} 0.122 μg ml^{-1}) [3], HL-60 cells [4], and P-388 murine leukemia cells (IC_{50} 4.56 μg ml^{-1}) [5]. Furthermore, it was established that the biological profile of these pyran-2-ones profoundly depends on the relative configuration of contiguous stereogenic centers. By virtue of significant activities of these molecules, impressive synthetic strategies have been reported. To date, most strategies rely on generation of chirality resulting from chiral synthons [6], asymmetric epoxidation [7], asymmetric alkoxyallylboration [8], proline-catalyzed aminoxylation [9], and chemoenzymatic synthesis [10]. Analysis of existing synthetic strategies of (2-phenylethyl)pyran-2-ones reveal that they lack in flexibility in terms of chemical

modification as well as suffer from moderate diastereoselectivities due to poor stereocontrol of substrate or reagent.

Results and Discussion. – In the course of our program aiming at developing flexible approaches for synthesizing different stereoisomers of biologically active small molecules [11], herein, we report an alternative highly diastereoselective strategy for the syntheses of (+)-7-epigoniodiol, (−)-8-epigoniodiol, and (+)-9-deoxygoniopypyrone by means of catalytic asymmetric hydroxylation, base-mediated chiral aldol reaction and ring-closing metathesis [12] as key steps. Our retrosynthetic analysis is delineated in *Scheme 1*.

Scheme 1. *Retrosynthetic Analysis of Target Molecule*

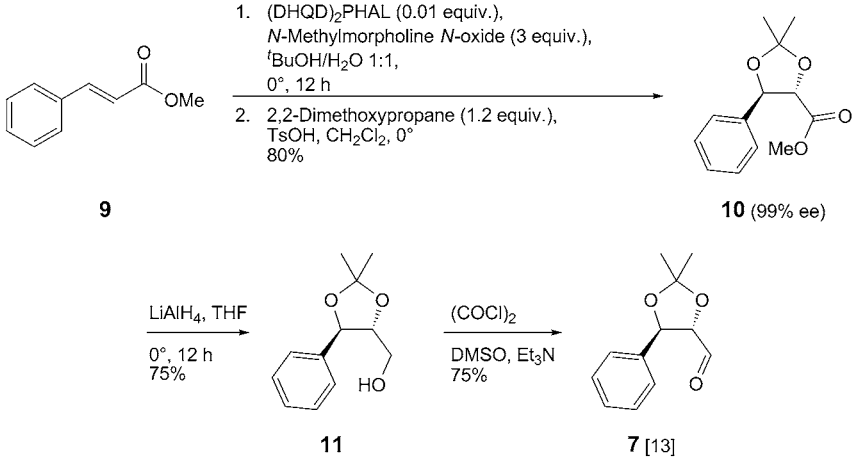


Initially, we envisaged to secure 5,6-dihydro-2*H*-pyran-2-one ring-closing metathesis (RCM) of homoallylic tethered ester with acrylate **5**. Then, two of three stereogenic centers in **1a**, the C(6) and C(7), were expected to arise from highly diastereoselective base-mediated chiral aldol reaction of 1-acetyloxazolidin-2-one **8d** to duly protected aldehyde **7**. The *syn*-dihydroxy moiety was anticipated to be generated through a asymmetric hydroxylation of methyl cinnamate **9** employing a respective chirality-inducing ligand (*Scheme 1*).

Accordingly, methyl cinnamate (**9**) was subjected to asymmetric hydroxylation with hydroquinidine phthalazine-1,4-diyl diether (=$(DHQD)_2PHAL$) and subsequent protection of the resulting diol with 2,2-dimethoxypropane under acidic conditions leading to **10** in 80% yield with 99% enantiomer purity. A two-step sequence of reduction, followed by oxidation, furnished aldehyde **7** in 56% yield [13] (*Scheme 2*).

With access to aldehyde **7**, we intended to explore the asymmetric aldol addition reaction. At the outset, we aimed at the evaluation of the stereochemical outcome of substrate-induced diastereoselectivity employing lithium enolate of AcOEt, **8a**. Thus, the reaction with **7** at $-78°$ led to the desired product **6a** with poor dr in 80% yield (*Table*, *Entry 1*). On the other hand, considerable improvement in dr was observed

Scheme 2. *Synthesis of Chiral Aldehyde* **7**



replacing the enolate of **8a** by the lithum enolate of 1-acetyloxazolidinone, **8b**, under similar conditions (*Table*, *Entry 2*). As well, employing the enolate of *N*,*O*-dimethylhydroxylacetamide, **8c**, in the reaction with **7** did not improve the dr of **6c** (*Table*, *Entry 3*).

Eventually, the addition of the lithium enolate of 1-acetyloxazolidinone, **8d**, [14] to aldehyde **7** resulted in the required compound **6d** in $>99\%$ diastereomeric purity with good yield[1]) [15] (*Table*, *Entry 4*), whereas the enolate of sultam **8e** led to a diminished dr with 70% yield (*Table*, *Entry 5*).

The high diastereoselectivity of the formation of **6d** could be rationalized on the basis of a six-membered chelate of the closed transition state **B*** (*Zimmerman–Traxler*) in which the **R** and **Xc** groups are in antiperiplanar position, and the diastereoface of the aldehyde efficiently shield by the benzyl moiety of the chiral auxiliary. In the case of **6a**, **6b**, and **6c**, due to the lower energy barrier between **A*** and **B*** transition states (*Fig. 2*), the minor conformer also leads to product, hence the lower diastereoselectivity was observed.

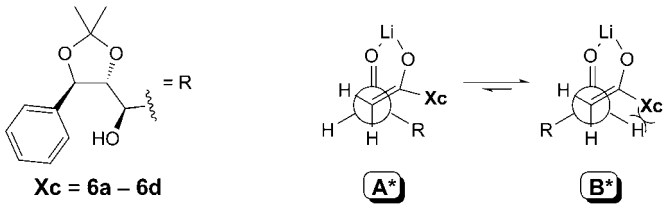
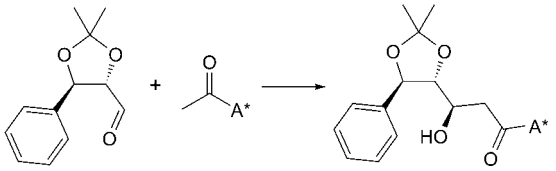


Fig. 2. *Transition states of Li-enolate addition to aldehyde* **7**

[1]) The *anti*/*syn* diastereoisomers were separated by CC (SiO_2; hexane/AcOEt). The enantioselectivity and relative configuration of the major compounds **6d** and **17** were determined on the basis of optical rotation value of final products **1a** and **1b**, respectively.

Table. *Additions of Various Acyl Enolates to Chiral Aldehyde* **7**



7 **8a – 8e** **6a – 6e**

Entry	**8**	A*	Conditions	**6**[b])	dr[c])	Yield [%]
1	**8a**	EtO	LDA[a]), THF, −78°, 2 h	**6a**	3:2	80
2	**8b**	2-Oxo-1,3-oxazolidin-3-yl	LDA, THF, −78°, 4 h	**6b**	4:1	80
3	**8c**	Methoxy(methyl)amino	LDA, THF, −78°, 3 h	**6c**	4:1	75
4	**8d**	(4*R*)-4-Benzyl-2-oxo-1,3-oxazolidin-3-yl	LDA, THF, −78°, 4 h	**6d**	>99	80
5	**8e**	(3a*S*,6*S*)-Tetrahydro-8,8-dimethyl-2,2-dioxido-3a,6-methano-2,1-benzothiazol-1(3*H*,4*H*)-yl	LDA, THF, −78°, 4 h	**6e**	>4:1	70

[a]) Lithium diisopropylamide (LiN(i-Pr)$_2$). [b]) Yields of isolated products. [c]) Diastereoisomer ratio determined by ^{1}H-NMR.

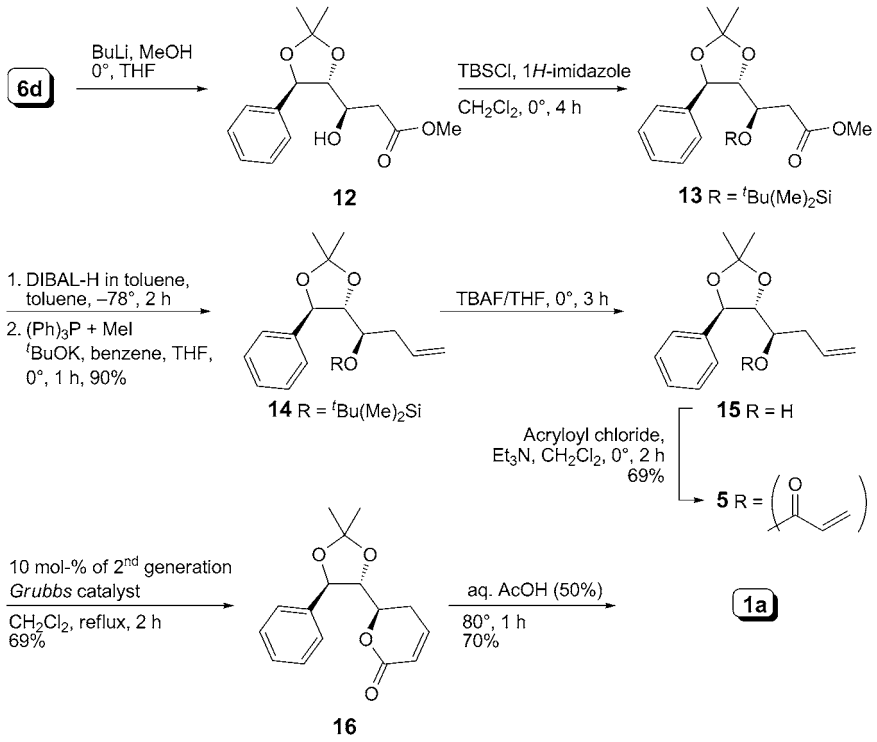
Methanolysis of enantiomerically pure **6d** with MeOLi (BuLi + MeOH, 0°, THF) provided **12** in 82% yield, and subsequent protection of secondary alcohol (^{t}Bu(Me)$_2$-SiCl, 1*H*-imidazole, CH_2Cl_2, r.t.) led to **13** (90%). Next, the ester was converted to the aldehyde, followed by olefination, resulting in the protected homoallylic alcohol **14** (90%). Fluoride ion induced deprotection of the silyl ether and subsequent reaction of the resulting secondary alcohol with acryloyl chloride under basic conditions furnished **5** in 69% yield (*Scheme 3*).

Finally, RCM led to the target compound **1a** in 71% yield. The spectroscopic data and specific rotation of **1a** are in full agreement with those reported in the literature ($[\alpha]_D^{20} = +85.0$ ($c = 0.3$, MeOH); [15]: $[\alpha]_D^{20} = +85.4$ ($c = 0.3$, MeOH)).

Under similar conditions, the reaction between *ent*-aldehyde **7** and **8d** resulted in **17** (60% yield), but in low diastereoselectivity (8:2)[1]). This could be rationalized on the basis of mismatched effect as evident in enol additions to aldehydes. Further, the amide was transformed to the methyl ester, followed by protection with TBDMSCl, to give **19** (70% over two steps). Reduction of the ester to the aldehyde, followed by *Wittig* olefination, led to **20**. Removal of the protecting group and subsequent reaction with acryloyl chloride gave **22** in 71% yield. Exposure of **22** to RCM, followed by acid-mediated isomerization, resulted in the isomer 8-epigoniodiol (**1b**) in 71% yield. Finally, DBU-catalyzed intramolecular addition of **1b** led 9-deoxygoniopypyrone (**4**) in 86% yield (*Scheme 4*). The analytical data of **1b** and **4** were in full agreement with the data reported for the natural product [3][5].

Conclusions. – We succeeded in developing a unified stereochemical diversity-oriented synthesis for styryl lactones, a class of natural products. The consecutive OH motif that is either *syn*,*syn* or *syn*,*anti* was generated with high stereocontrol and a

Scheme 3. *Synthesis of the Target Molecule.* DIBAL-H, Diisobutylaluminium hydride; TBAB, Bu_4NF.



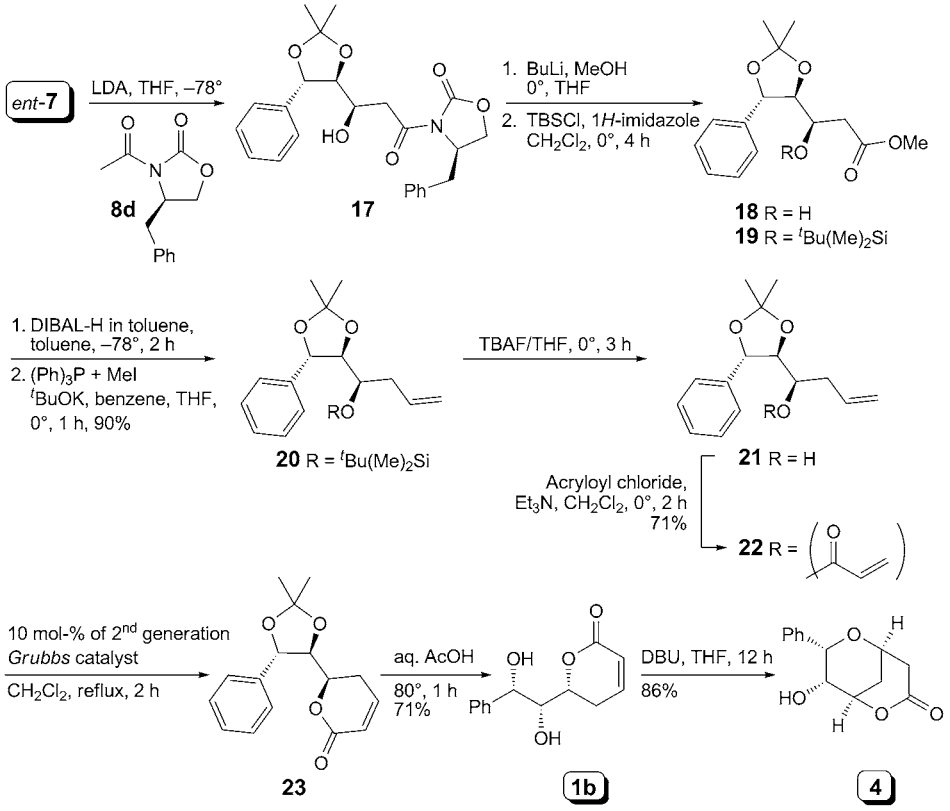
predictable relative configuration through a catalytic hydroxylation and base-mediated 1-acetyloxazolidinone addition reactions. Employing the key reaction, followed by application of established chemistry, could allow skeletal and stereogenic diversity, which can generate a library of analogs. Research on further applications of this strategy for the synthesis of biologically active compounds bearing a OH motif is underway.

Experimental Part

General. All reactions were conducted under N_2 (*IOLAR* Grade I). Glassware used for reactions were oven-dried, and THF was distilled over sodium benzophenone ketyl before use. All other chemicals used were commercially available. Progress of the reactions was monitored by TLC on precoated *Silica Gel 60 F-254* plates. Evaporation of solvents was performed at reduced pressure on a rotary evaporator. Column chromatography (CC): silica gel, grade 60–120, or 100–200 mesh. Optical rotations: *Horiba* high-sensitive polarimeter; 10-mm cell. IR Spectra: *Thermo-Nicolet-FT/IR-5700* instrument; $\tilde{\nu}$ in cm^{-1}. ^1H- and ^{13}C-NMR Spectra: *Varian 200* and *500*, *Bruker 300* and *400*, at 300, 400, and 500 MHz (^1H), and 75 or 100 MHz (^{13}C); in $CDCl_3$; δ in ppm rel. to Me_4Si as internal standard, J in Hz. ESI- and HR-MS: quadrupole time-of-flight (QTOF) mass spectrometer *QSTAR XL* (*Applied Biosystems MDSSciex*, Foster City, USA); in *m/z*.

*(4*R*)-4-Benzyl-3-[(3*R*)-3-[(4*R*,5*R*)-2,2-dimethyl-5-phenyl-1,3-dioxolan-4-yl]-3-hydroxypropanoyl]-1,3-oxazolidin-2-one* (**6d**). Anh. THF (24 ml) was introduced into a 250-ml flask under inert atmosphere,

Scheme 4. *Synthesis of 9-Deoxygoniopypyrone* (**4**). DBU, 1,8-Diazabicycloundec-7-ene.



and $^{i}Pr_2NH$ (4.8 mmol) and BuLi (1.6M/hexane, 4.4 mmol) were sequentially added at $-78°$. Thereafter, a THF soln. (24 ml) of *(4*R*)-3-acetyl-4-benzyl-1,3-oxazolidin-2-one* (**8d**; 876 mg, 4.0 mmol) was added over 30 min, and the resulting soln. was stirred for another 10 min. Then, a THF soln. (40 ml) of *(4*S*,5*R*)-2,2-dimethyl-5-phenyl-1,3-dioxolane-4-carbaldehyde* (**7**; 865 mg, 4.4 mmol) was added during 2 h with syringe pump at $-78°$. The resulting mixture was stirred further for 4 h at the same temp., followed by quenching the reaction with sat. aq. NH_4Cl soln. The aq. layer was extracted with CH_2Cl_2 (3×60 ml), and the combined org. layers were dried (Na_2SO_4). Removal of the solvent under reduced pressure gave a crude residue, which was purified by CC (hexane/AcOEt 7:3) to give **6d** (1.5 g, 80%). Colorless liquid. $[\alpha]_D^{24} = +3.0$ ($c = 0.9$, $CHCl_3$). IR (KBr): 3420, 2969, 2924, 1739, 1452, 1368, 1215, 1058, 760, 700, 681. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.54–7.13 (*m*, 10 H); 4.99 (*d*, $J = 7.9$, 1 H); 4.62–4.53 (*m*, 1 H); 4.39–4.31 (*m*, 1 H); 4.22–4.02 (*m*, 3 H); 3.30–3.14 (*m*, 3 H); 2.98 (br. *s*, 1 H); 2.76 (*dd*, $J = 12.8, 9.8$, 1 H); 1.56 (*s*, 3 H); 1.51 (*s*, 3 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 171.7; 153.2; 138.3; 134.9; 129.3; 129.0; 128.4; 128.2; 127.4; 109.5; 84.2; 80.4; 68.3; 66.2; 55.0; 39.0; 37.7; 29.6; 27.3; 27.0. ESI-MS: 448 ($[M + Na]^+$). HR-ESI-MS: 448.1715 ($[M + Na]^+$, $C_{24}H_{27}NNaO_6^+$; calc. 448.1736).

*Methyl (3*R*)-3-[(4*R*,5*R*)-2,2-Dimethyl-5-phenyl-1,3-dioxolan-4-yl]-3-hydroxypropanoate* (**12**). BuLi (1.6M/hexane, 4.4 mmol) and MeOH (2 ml) was added sequentially to anh. THF (16 ml) at 0°. Then, a THF (15 ml) soln. of **6d** (1.25 g, 2.94 mmol) was added, and the resulting mixture was stirred for 1 h. Then, the reaction was quenched with sat. aq. NH_4Cl soln., and the resulting slurry was extracted with CH_2Cl_2 (3×30 ml). The combined org. layers were dried (Na_2SO_4). The solvent was removed under reduced pressure to give a crude residue, which was purified by CC (hexane/AcOEt 7:3) to yield **12**

(674 mg, 82%). Colorless liquid. $[\alpha]_D^{24} = -4.5$ ($c = 0.9$, $CHCl_3$). IR (KBr): 3464, 2924, 253, 1738, 1439, 1215, 1165, 1062, 887, 758, 700. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.41–7.20 (*m*, 5 H); 4.88 (*d*, *J* = 8.1, 1 H); 4.19–4.11 (*m*, 1 H); 3.85 (*dd*, *J* = 8.1, 5.6, 1 H); 3.59 (*s*, 3 H); 2.95 (br. *s*, 1 H); 2.53–2.38 (*m*, 2 H); 1.47 (*s*, 3 H); 1.41 (*s*, 3 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 172.8; 138.4; 128.5; 12.2; 127.2; 109.5; 84.4; 80.4; 68.5; 51.8; 37.3; 29.6; 27.2; 27.0. ESI-MS: 303 ($[M+Na]^+$). HR-ESI-MS: 303.1219 ($[M+Na]^+$, $C_{15}H_{20}NaO_5^+$; calc. 303.1208).

*Methyl (3*R*)-3-{[(*tert*-Butyl)(dimethyl)silyl]oxy}-3-[(4*S*,5*R*)-2,2-dimethyl-5-phenyl-1,3-dioxolan-4-yl]propanoate* (**13**). To a stirred soln. of **12** (630 mg, 2.25 mmol) in CH_2Cl_2 (15 ml) at 0° was added 1*H*-imidazole (204 mg, 3 mmol) and 4-(dimethylamino)pyridine (DMAP; cat.). ^{t}BuMe$_2$SiCl (TBDMSCl; 3 mmol) dissolved in CH_2Cl_2 was added, and the resulting soln. was stirred at r.t. for 4 h. Then, H_2O (20 ml) was added to the mixture, and the aq. layer was extracted with AcOEt (3 × 30 ml), dried, and filtered. The org. layer was evaporated under reduced pressure to give a crude residue, which was purified by CC (hexane/AcOEt 9:1) to give **13** (800 mg, 90%). Colorless liquid. $[\alpha]_D^{24} = +12.0$ ($c = 0.9$, $CHCl_3$). IR (KBr): 3033, 2986, 2858, 2113, 1694, 1374, 1253, 1065, 836, 778. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.45–7.29 (*m*, 5 H); 4.86 (*d*, *J* = 8.1, 1 H); 4.45–4.36 (*m*, 1 H); 3.98 (*dd*, *J* = 8.1, 2.8, 1 H); 3.60 (*s*, 3 H); 2.48–2.27 (*m*, 2 H); 1.52 (*s*, 3 H); 1.49 (*s*, 3 H); 0.84 (*s*, 9 H); 0.02 (*s*, 3 H); 0.01 (*s*, 3 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 171.7; 138.2; 128.5; 128.3; 127.3; 109.1; 85.5; 79.0; 68.3; 51.5; 39.1; 27.2; 25.4; 17.9; −4.4; −5.0. ESI-MS: 417 ($[M+Na]^+$). HR-ESI-MS: 417.2075 ($[M+Na]^+$, $C_{21}H_{34}NaO_5Si^+$; calc. 417.2073).

*(*tert*-Butyl)({(1*R*)-1-[(4*S*,5*R*)-2,2-dimethyl-5-phenyl-1,3-dioxolan-4-yl]but-3-en-1-yl}oxy)dimethylsilane* (**14**). Compound **13** (680 mg, 1.72 mmol) was dissolved in toluene (15 ml), and the soln. was cooled to −78°. Then, DIBAL-H (1.18 ml, 1.6M in toluene, 1.89 mmol) was added, and the resulting mixture was stirred at the same temp. After 2 h, the reaction was quenched with sat. aq. potassium sodium tartarate. The resulting mixture was diluted with AcOEt and stirred vigorously at r.t. until the layers became clear. The org. layer was separated and washed with brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure to give the crude aldehyde. To a separate flask, (methyl)(triphenyl)phosphonium iodide (964 mg, 2.41 mmol) and ^{t}BuOK (195 mg, 1.76 mmol) was added. To this, dry THF (10 ml) was added while stirring, and stirring was continued further for 4 h at r.t. Stirring was stopped, and the solid was allowed to settle, the clear supernant orange-yellow liquid was then cannulated into the THF (5 ml) soln. of the above crude aldehyde (600 mg, 1.6 mmol) at 0°. Then, the mixture was stirred at the same temp. for 15 min. The reaction was quenched with aq. sat. NH_4Cl, and the mixture was extracted with AcOEt (3 × 30 ml). The org. layer was removed under reduced pressure to give a crude residue, which was purified by CC (hexane/AcOEt 9:1) to yield **14** (540 mg, 90%). Colorless liquid. $[\alpha]_D^{24} = +7.5$ ($c = 0.9$, $CHCl_3$). IR (KBr): 3074, 2934, 2860, 1637, 1447, 1374, 1246, 1063, 833, 769. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.44–7.22 (*m*, 5 H); 5.56 (*m*, 1 H); 4.98–4.83 (*m*, 2 H); 4.60 (*d*, *J* = 17.1, 1 H); 3.99–3.87 (*m*, 2 H); 2.22–1.89 (*m*, 2 H); 1.49 (*s*, 3 H); 1.47 (*s*, 3 H); 0.91 (*s*, 9 H); 0.07 (*s*, 3 H); 0.06 (*s*, 3 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 134.0; 133.8; 133.6; 128.7; 128.5; 128.4; 128.2; 127.7; 117.4; 108.5; 84.2; 78.5; 71.0; 38.8; 27.4; 27.3; 25.9; 18.1; −4.3; −4.6. ESI-MS: 385 ($[M+Na]^+$). HR-ESI-MS: 385.2175 ($[M+Na]^+$, $C_{21}H_{34}NaO_3Si^+$; calc. 385.2175).

*(1*R*)-1-[(4*R*,5*R*)-2,2-Dimethyl-5-phenyl-1,3-dioxolan-4-yl]but-3-en-1-ol* (**15**). To a cooled (0°) soln. of THF (10 ml) containing **14** (500 mg, 1.38 mmol), Bu_4NF (1.51 ml, 1M in THF, 1.51 mmol) was added, and the mixture was stirred for 2 h at r.t. The reaction was quenched with H_2O (3 ml), and the mixture was extracted with AcOEt (3 × 30 ml). The solvent was removed under reduced pressure to give a residue, which was purified by CC (hexane/AcOEt 6:4) to yield pure **15** (320 mg, 93%). Colorless liquid. $[\alpha]_D^{24} = +2.0$ ($c = 0.9$, $CHCl_3$). IR (KBr): 3457, 3035, 2985, 2929, 1640, 1375, 1236, 1058, 806, 757, 699. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.45–7.24 (*m*, 5 H); 5.74–5.59 (*m*, 1 H); 4.97–4.95 (*m*, 2 H); 4.86 (*dd*, *J* = 17.1, 1.5, 1 H); 3.91–3.83 (*m*, 2 H); 2.17–2.12 (*m*, 2 H); 2.02 (br. *s*, 1 H); 1.54 (*s*, 3 H); 1.49 (*s*, 3 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 133.8; 128.4; 128.3; 127.6; 126.8; 118.2; 109.0; 84.6; 79.3; 70.4; 37.2; 27.2; 27.0. ESI-MS: 271 ($[M+Na]^+$). HR-ESI-MS: 271.1312 ($[M+Na]^+$, $C_{15}H_{20}NaO_3^+$; calc. 271.1310).

*(1*R*)-1-[(4*R*,5*R*)-2,2-Dimethyl-5-phenyl-1,3-dioxolan-4-yl]but-3-en-1-yl Prop-2-enoate* (**5**). To a stirred CH_2Cl_2 (8 ml) soln. containing **15** (300 mg, 1.2 mmol) was added Et_3N (0.186 ml, 1.34 mmol), followed by acryloyl chloride (0.116 ml, 1.44 mmol) at 0°, and the mixture was stirred for 2 h at the same temp. Then, the reaction was quenched with sat. aq. $NaHCO_3$ soln., and the mixture was extracted with

AcOEt (3×15 ml). The combined org. layers were washed with H_2O, dried (Na_2SO_4), and filtered. Solvent was removed under reduced pressure to give a crude residue, which was purified by CC (hexane/AcOEt 8:2) to give **5** (270 mg, 74%). Colorless liquid. $[\alpha]_D^{24} = +40.0$ ($c = 0.9$, $CHCl_3$). IR (KBr): 2961, 2925, 1730, 1631, 1407, 1260, 1025, 802, 697. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.36–7.23 (*m*, 5 H); 6.23–6.14 (*m*, 1 H); 5.95–5.83 (*m*, 1 H); 5.73–5.55 (*m*, 2 H); 5.26–5.17 (*m*, 1 H); 4.99–4.80 (*m*, 3 H); 3.99 (*dd*, $J = 6.2$, 8.1, 1 H); 2.46–2.21(*m*, 2 H); 1.50 (*s*, 3 H); 1.42 (*s*, 3 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 137.7; 132.7; 131.2; 128.5; 128.4; 127.9; 127.5; 118.2; 109.6; 82.8; 80.7; 72.5; 35.6; 29.7; 27.2; 26.8. ESI-MS: 325 ($[M + Na]^+$). HR-ESI-MS: 325.1419 ($[M + Na]^+$, $C_{18}H_{22}NaO_4^+$; calc. 325.1416).

*(6*R*)-6-[(4*R*,5*R*)-2,2-Dimethyl-5-phenyl-1,3-dioxolan-4-yl]-5,6-dihydro-2*H*-pyran-2-one* (**16**). Compound **5** (250 mg, 0.82 mmol) was dissolved in dry CH_2Cl_2 (8 ml), and *Grubbs* (second generation) catalyst was added (reflux for 2 h). Then, the solvent was removed under reduced pressure to give a residue, which was purified by CC (hexane/AcOEt 8:2) to yield pure **16** (180 mg, 69%). Colorless liquid. $[\alpha]_D^{24} = +58.2$ ($c = 0.9$, $CHCl_3$). IR (KBr): 2922, 2854, 1728, 1629, 1458, 1378, 1248, 1075. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.48–7.30 (*m*, 5 H); 6.93–6.85 (*m*, 1 H); 6.04–5.97 (*m*, 1 H); 4.99 (*d*, $J = 7.7$, 1 H); 4.60–4.51 (*m*, 1 H); 4.12 (*dd*, $J = 7.7$, 5.4, 1 H); 2.60–2.42 (*m*, 2 H); 1.58 (*s*, 3 H); 1.52 (*s*, 3 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 162.9; 144.6; 137.8; 128.6; 128.5; 127.0; 121.4; 110.2; 83.0; 80.5; 77.4; 27.2; 27.0; 25.6. ESI-MS: 297 ($[M + Na]^+$). HR-ESI-MS: 297.1103 ($[M + Na]^+$, $C_{16}H_{18}NaO_4^+$; calc. 297.1103).

(+)-7-Epigoniodiol (=*(6*R*)-6-[(1*S*,2*R*)-1,2-Dihydroxy-2-phenylethyl]-5,6-dihydro-2*H*-pyran-2-one*; **1a**). Pyranone **16** (150 mg, 0.54 mmol) was dissolved in 50% aq. AcOH (10 ml) and heated at 80° for 1 h. H_2O (20 ml) was added, the mixture was extracted with AcOEt, and the org. layer washed with sat. $NaHCO_3$ soln. The org. solvent was removed under vacuum, and the resulting residue was purified by CC (hexane/AcOEt 2:8) to yield **1a** (90 mg, 70%). Colorless liquid. $[\alpha]_D^{20} = +85.0$ ($c = 0.3$, MeOH); [15]: $[\alpha]_D^{20} = +85.4$ ($c = 0.3$, MeOH). IR (KBr): 3448, 2924, 1704, 1629, 1391, 1261, 1081, 1029, 808, 710. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.38–7.31 (*m*, 5 H); 6.93–6.91 (*m*, 1 H); 6.00 (*dd*, $J = 9.7$, 1.0, 1 H); 4.90 (*d*, $J = 4.1$, 1 H); 4.42–4.38 (*m*, 1 H); 3.95–3.93 (*m*, 1 H); 2.83 (br. *s*, 1 H); 2.80 (br. *s*, 1 H); 2.61–2.59 (*m*, 1 H); 2.49 (*ddd*, $J = 18.8$, 5.2, 4.9, 1 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 163.8; 145.6; 140.1; 128.7; 126.4; 120.9; 77.3; 76;1; 71.9; 24.9. ESI-MS: 257 ($[M + Na]^+$). HR-ESI-MS: 257.0796 ($[M + Na]^+$, $C_{13}H_{14}NaO_4^+$; calc. 257.0790).

*(4*R*)-4-Benzyl-3-{(3*R*)-3-[(4*S*,5*S*)-2,2-dimethyl-5-phenyl-1,3-dioxolan-4-yl]-3-hydroxypropanoyl}-1,3-oxazolidin-2-one* (**17**). Yield: 60%. Colorless liquid. $[\alpha]_D^{24} = +5.0$ ($c = 0.9$, $CHCl_3$). IR (KBr): 3420, 2969, 2924, 1739, 1452, 1368, 1215, 1058, 760, 700, 681. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.54–7.15 (*m*, 10 H); 5.00 (*d*, $J = 8.0$, 1 H); 4.69–4.62 (*m*, 1 H); 4.40–4.33 (*m*, 1 H); 4.25–4.00 (*m*, 3 H); 3.30–3.12 (*m*, 3 H); 2.94 (br. *s*, 1 H); 2.69 (*dd*, $J = 13.0$, 10.0, 1 H); 1.56 (*s*, 3 H); 1.51 (*s*, 3 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 171.8; 153.2; 138.5; 135.1; 129.3; 128.9; 128.5; 128.2; 127.3; 109.6; 84.5; 80.5; 77.4; 77.0; 76.5; 68.5; 66.3; 55.0; 38.9; 37.8; 27.3; 27.0. ESI-MS: 448 ($[M + Na]^+$). HR-ESI-MS: 448.1715 ($[M + Na]^+$, $C_{24}H_{27}NNaO_6^+$; calc. 448.1736).

*Methyl (3*R*)-3-[(4*S*,5*S*)-2,2-Dimethyl-5-phenyl-1,3-dioxolan-4-yl]-3-hydroxypropanoate* (**18**). Yield: 87%. Colorless liquid. $[\alpha]_D^{24} = +7.5$ ($c = 0.9$, $CHCl_3$). IR (KBr): 3464, 2924, 253, 1738, 1439, 1215, 1165, 1062, 887, 758, 700. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.25–7.15 (*m*, 5 H); 5.02 (*d*, $J = 7.7$, 1 H); 4.29–4.23 (*m*, 1 H); 3.91 (*dd*, $J = 7.7$, 5.8, 1 H); 3.53 (*s*, 3 H); 3.05 (br. *s*, 1 H); 2.37–2.27 (*m*, 2 H); 1.56 (*s*, 3 H); 1.54 (*s*, 3 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 166.4; 136.7; 128.5; 126.8; 110.1; 84.3; 79.6; 65.1; 52.0; 29.6; 27.2; 26.9. ESI-MS: 303 ($[M + Na]^+$). HR-ESI-MS: 303.1219 ($[M + Na]^+$, $C_{15}H_{20}NaO_5^+$; calc. 303.1208).

*Methyl (3*R*)-3-{[(*tert*-Butyl)(dimethyl)silyl]oxy}-3-[(4*R*,5*S*)-2,2-dimethyl-5-phenyl-1,3-dioxolan-4-yl]propanoate* (**19**). Yield: 85%. Colorless liquid. $[\alpha]_D^{24} = +11.1$ ($c = 0.9$, $CHCl_3$). IR (KBr): 3033, 2986, 2858, 2113, 1694, 1374, 1253, 1065, 836, 778. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.40–7.27 (*m*, 5 H); 4.82 (*d*, $J = 8.3$, 1 H); 4.40–4.31 (*m*, 1 H); 3.90 (*dd*, $J = 8.3$, 4.5, 1 H); 3.64 (*s*, 3 H); 2.57 (*dd*, $J = 15.8$, 4.5, 1 H); 2.39 (*dd*, $J = 15.8$, 7.5, 1 H); 1.52 (*s*, 3 H); 1.48 (*s*, 3 H); 0.78 (*s*, 9 H); 0.04 (*s*, 3 H); –0.05 (*s*, 3 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 171.7; 138.1; 128.5; 128.2; 127.5; 109.0; 84.7; 79.1; 69.0; 51.4; 38.8; 29.7; 27.2; 27.0; 25.7; 18.0; –4.5; –5.1. ESI-MS: 417 ($[M + Na]^+$). HR-ESI-MS: 417.2075 ($[M + Na]^+$, $C_{21}H_{34}NaO_5Si^+$; calc. 417.2073).

*(*tert*-Butyl)({(1*R*)-1-[(4*R*,5*S*)-2,2-dimethyl-5-phenyl-1,3-dioxolan-4-yl]but-3-en-1-yl}oxy)dimethylsilane* (**20**). Yield: 87%. Colorless liquid. $[\alpha]_D^{24} = +4.4$ ($c = 0.9$, $CHCl_3$). IR (KBr): 3074, 2934, 2860, 1637, 1447, 1374, 1246, 1063, 833, 769. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.38–7.23 (*m*, 5 H); 5.73–5.63 (*m*, 1 H);

4.97–4.83 (*m*, 3 H); 3.84 (*dd*, *J* = 8.0, 4.0, 1 H); 3.80–3.75 (*m*, 1 H); 2.43–2.35 (*m*, 1 H); 2.21–2.13 (*m*, 1 H); 1.51 (*s*, 3 H); 1.48 (*s*, 3 H); 0.85 (*s*, 9 H); 0.07 (*s*, 3 H); 0.02 (*s*, 3 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 138.3; 134.5; 128.4; 128.1; 127.4; 126.3;117.3; 108.7; 84.5; 79.0; 71.8; 38.5; 29.6; 27.3; 27.1; 25.9; 18.1; −4.2; −4.3. ESI-MS: 385 ([*M* + Na]$^+$). HR-ESI-MS: 385.2175 ([*M* + Na]$^+$, $C_{21}H_{34}NaO_3Si^+$; calc. 385.2175).

*(1*R*)-1-[(4*S*,5*S*)-2,2-Dimethyl-5-phenyl-1,3-dioxolan-4-yl]but-3-en-1-ol* (**21**). Yield: 90%. Colorless liquid. $[\alpha]_D^{24} = +7.2$ (*c* = 0.9, $CHCl_3$). IR (KBr): 3457, 3035, 2985, 2929, 1640, 1375, 1236, 1058, 806, 757, 699. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.40–7.24 (*m*, 5 H); 5.80–5.69 (*m*, 1 H); 5.06–4.98 (*m*, 3 H); 4.94 (*d*, *J* = 9.0, 1 H); 3.70–3.54 (*m*, 2 H); 2.33–2.17 (*m*, 2 H); 1.96 (*d*, *J* = 9.0, 1 H); 1.55 (*s*, 3 H); 1.50 (*s*, 3 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 137.6; 134.1; 128.6; 128.3; 126.9; 117.8; 109.3; 85.0; 79.3; 68.1; 39.6; 29.6; 27.3; 27.0. ESI-MS: 271 ([*M* + Na]$^+$). HR-ESI-MS: 271.1312 ([*M* + Na]$^+$, $C_{15}H_{20}NaO_3^+$; calc. 271.1310).

*(1*R*)-1-[(4*S*,5*S*)-2,2-Dimethyl-5-phenyl-1,3-dioxolan-4-yl]but-3-en-1-yl Prop-2-enoate* (**22**). Yield: 71%. Colorless liquid. $[\alpha]_D^{24} = -76.5$ (*c* = 0.9, $CHCl_3$). IR (KBr): 2961, 2925, 1730, 1631, 1407, 1260, 1025, 802, 697. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.44–7.28 (*m*, 5 H); 6.50–6.46 (*m*, 1 H); 6.23–6.14 (*m*, 1 H); 5.88 (*d*, *J* = 11.1, 1 H); 5.71–5.60 (*m*, 1 H); 5.17–4.98 (*m*, 3 H); 4.73 (*d*, *J* = 8.8, 1 H); 3.90 (*dd*, *J* = 8.8, 2.2, 1 H); 2.56–2.38 (*m*, 2 H); 1.58 (*s*, 3 H); 1.51 (*s*, 3 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 165.6; 137.3; 132.9; 131.4; 128.6; 128.3; 128.1; 126.7; 118.3; 109.4; 83.5; 78.8; 69.4; 36.3; 29.6; 27.1; 26.7. ESI-MS: 325 ([*M* + Na]$^+$). HR-ESI-MS: 325.1419 ([*M* + Na]$^+$, $C_{18}H_{22}NaO_4^+$; calc. 325.1416).

*(6*R*)-6-[(4*S*,5*S*)-2,2-Dimethyl-5-phenyl-1,3-dioxolan-4-yl]-5,6-dihydro-2*H*-pyran-2-one* (**23**). Yield: 65%. Colorless liquid. $[\alpha]_D^{24} = -95.1$ (*c* = 0.9, $CHCl_3$). IR (KBr): 2922, 2854, 1728, 1629, 1458, 1378, 1248, 1075. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.50–7.30 (*m*, 5 H); 6.90–6.83 (*m*, 1 H); 6.03 (*d*, *J* = 9.7, 1 H); 5.24 (*d*, *J* = 8.5, 1 H); 4.45–4.38 (*m*, 1 H); 3.82 (*d*, *J* = 8.5, 1 H); 2.74–2.64 (*m*, 1 H); 2.25 (*ddd*, *J* = 23.2, 9.7, 4.9, 1 H); 1.59 (*s*, 3 H); 1.55 (*s*, 3 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 163.6; 144.7; 137.1; 128.7; 128.6; 126.8; 121.7; 110.0. ESI-MS: 297 ([*M* + Na]$^+$). HR-ESI-MS: 297.1103 ([*M* + Na]$^+$, $C_{16}H_{18}NaO_4^+$; calc. 297.1103).

(−)-8-Epigoniodiol (= *(6*R*)-6-[(1*R*,2*S*)-1,2-Dihydroxy-2-phenylethyl]-5,6-dihydro-2*H*-pyran-2-one*; **1b**). Yield: 71%. Colorless liquid. $[\alpha]_D^{25} = -13.7$ (*c* = 0.7, $CHCl_3$) ([3][5]: $[\alpha]_D^{25} = -13.7$ (*c* = 0.7, $CHCl_3$)). IR (KBr): 3448, 2924, 1704, 1629, 1391, 1261, 1081, 1029, 808, 710. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.47–7.28 (*m*, 5 H); 6.85 (*ddd*, *J* = 8.4, 6.3, 2.0, 1 H); 5.95 (*dd*, *J* = 9.8, 2.2, 1 H); 4.96 (*d*, *J* = 6.2, 1 H); 4.20 (*dd*, *J* = 12.6, 3.8, 1 H); 3.89–3.10 (*m*, 3 H); 2.83 (*ddt*, *J* = 18.6, 12.6, 2.7, 1 H); 2.09 (*ddd*, *J* = 18.7, 6.3, 3.9, 1 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 164.0; 146.0; 140.1; 128.7; 128.3; 126.9; 120.5; 77.0; 76.5; 74.1; 26.0. ESI-MS: 257 ([*M* + Na]$^+$). HR-ESI-MS: 257.0796 ([*M* + Na]$^+$, $C_{13}H_{14}NaO_4^+$; calc. 257.0790).

(+)-9-Deoxygoniopypyrone (= *(1*R*,5*R*,7*S*,8*S*)-8-Hydroxy-2,6-dioxa-7-phenylbicyclo[3.3.1]nonan-3-one*; **4**). DBU (0.008 ml, 0.06 mmol) was added to a soln. of **1b** (70 mg, 0.29 mmol) in 0.5 ml of THF. The mixture was stirred for 24 h at r.t., extracted with AcOEt, washed with H_2O, dried (Na_2SO_4), and purified by CC (hexane/AcOEt) to yield **4** (60 mg, 86%). Solid. $[\alpha]_D^{24} = +12.5$ (*c* = 0.2, EtOH) ([3][5]: $[\alpha]_D^{24} = +12.5$ (*c* = 0.2, EtOH)). IR (KBr): 3448, 2930, 2859, 1733, 1631, 1461, 1253, 1074, 830, 772, 731. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.43–7.31 (*m*, 5 H); 4.95 (br. *s*, 1 H); 4.86 (*m*, 1 H); 4.51 (*m*, 1 H); 3.94 (br. *s*, 1 H); 3.02–2.82 (*m*, 2 H); 2.63–2.56 (*ddd*, *J* = 14.1, 4.0, 1.1, 1 H); 1.84 (*dd*, *J* = 13.5, 3.4, 1 H); 1.65 (*d*, *J* = 3.3, 1 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 169.2; 136.7; 128.9; 18.4; 126.2; 74.2; 70.5; 68.3; 66.1; 36.3; 24.0. ESI-MS: 257 ([*M* + Na]$^+$). HR-ESI-MS: 257.0756 ([*M* + Na]$^+$, $C_{13}H_{14}NaO_4^+$; calc. 257.0790).

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