Stereoselective First Total Synthesis of a Ten-Membered Macrolide from L-Malic Acid and (2*R*)-2,3-*O*-Cyclohexylideneglyceraldehyde

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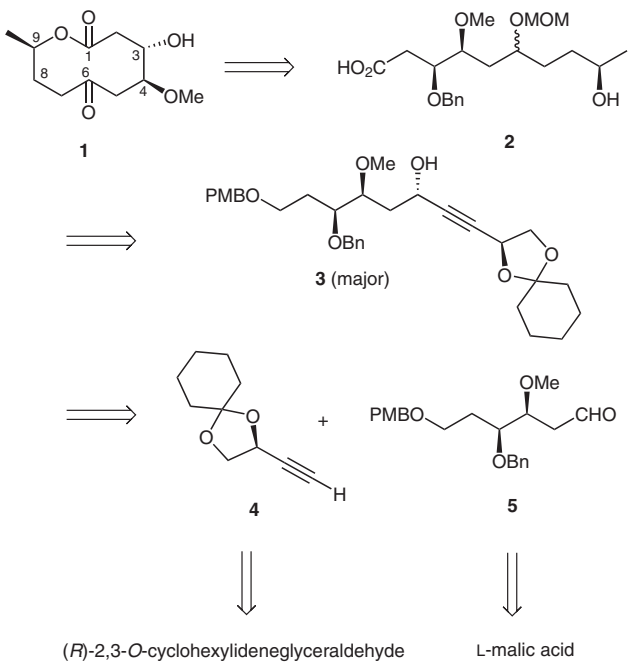
Abstract: A convergent stereoselective first total synthesis of a novel ten-membered macrolide from L-malic acid and (2*R*)-2,3-*O*-cyclohexylideneglyceraldehyde is reported.

Key words: ten-membered macrolide, (2*R*)-2,3-*O*-cyclohexylideneglyceraldehyde, L-malic acid, 1,2-*syn* allylation, Yamaguchi macrolactonization

Much current interest has been focused on the utility of naturally occurring bifidus factors and growth inhibitors against harmful bacteria such as *Clostridium* and *E. coli*. The ascomycetous genus *Cordyceps* is an entamopathogenic fungus that has found extensive use in food and herbal medicine in Asia. *Cordyceps* genus is a known rich source of biologically active secondary metabolites.[1] In recent years, these secondary metabolites have received attention due to their unique structure and specific biological activities.

Cardicepin (3′-deoxyadenosine), possessing antifungal, antiviral, and antitumour activities, is one of a few secondary metabolites previously isolated from *C. millitaris*. A novel ten-membered macrolide **1** (Scheme 1), structurally related to cephalosporolide C, was isolated from *Cordiceps militaris* BCC 2816 as one of the biologically active natural product possessing antimalarial activity against *Plasmodium falsifarum* K1 (multidrug-resistant strain).[2] Considering the fact that cyclizations of medium-ring lactones with n = 8–11 (n = number of carbon atoms in the lactone ring) are difficult to achieve due to enthalpy and entropy factors[3] and the intrinsic limitation that not all macrolides could be accessed through the Grubbs catalyst mediated ring-closing metathesis approach,[4] makes the ten-membered macrolide synthesis more so challenging. The impressive biological profile of **1** coupled with structural features, especially the strategically located 6-keto functionality attracted our attention. This paper describes the stereoselective first total synthesis of **1**.

In accordance with our interest in the natural product synthesis,[5] herein we report stereoselective first total synthesis of **1** by a convergent strategy wherein both the intermediates are drawn from the common, inexpensive starting materials, L-malic acid and (2*R*)-2,3-*O*-cyclohexylideneglyceraldehyde. Our strategy relies on chelation-controlled 1,2-*syn* allylation, acetylenic anion addition onto a chiral aldehyde, exhaustive reduction, and Yamaguchi macrolactonization as the key steps. Retrosynthetic analysis reveals that target compound **1** can be obtained from seco acid **2** by Yamaguchi macrolactonization followed by the selective deprotection of MOM ether, oxidation of the ensuing free hydroxyl group to its keto functionality, and subsequent deprotection of the benzyl group. Accordingly, to garner the requisite cabon chain with rightly positioned stereocenters, accessing seco acid **2** remains the most important task. Strategically, seco acid **2** could be obtained from chiral propargyl alcohol **3**. Compound **3**, in turn, could be obtained by coupling of fragments **4** and **5** followed by the functional group manipulations. Both fragments **4** and **5** are realized from (2*R*)-2,3-*O*-cyclohexylideneglyceraldehyde and L-malic acid, respectively, by simple chemical transformations.



Scheme 1 Retrosynthetic analysis of **1**

Accordingly, the synthesis of **1** starts with the preparation of alkyne **4** (Scheme 2). Thus, known[6a] (2*R*)-2,3-*O*-cyclohexylideneglyceraldehyde **6** was converted into an acetylenic functionality via the conventional vinyl dibromide (CBr_4, Ph_3P, THF, r.t.) and its subsequent exposure to EtMgBr to afford the alkyne **4** (60%).[6b]

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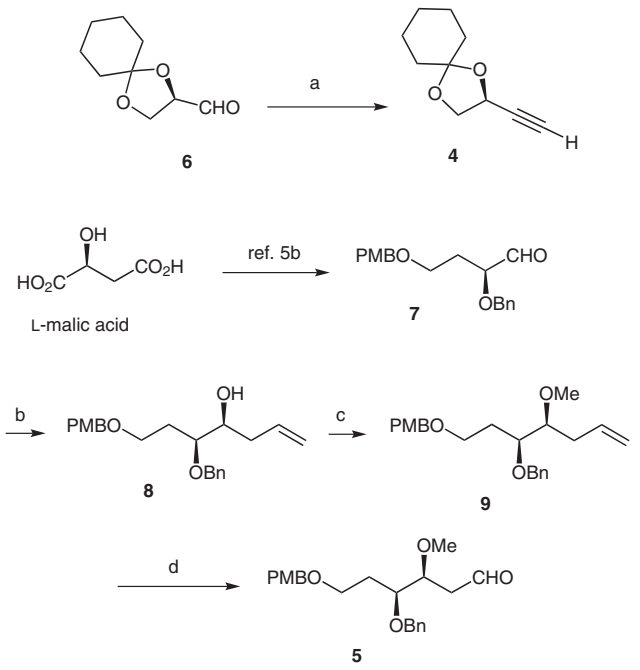
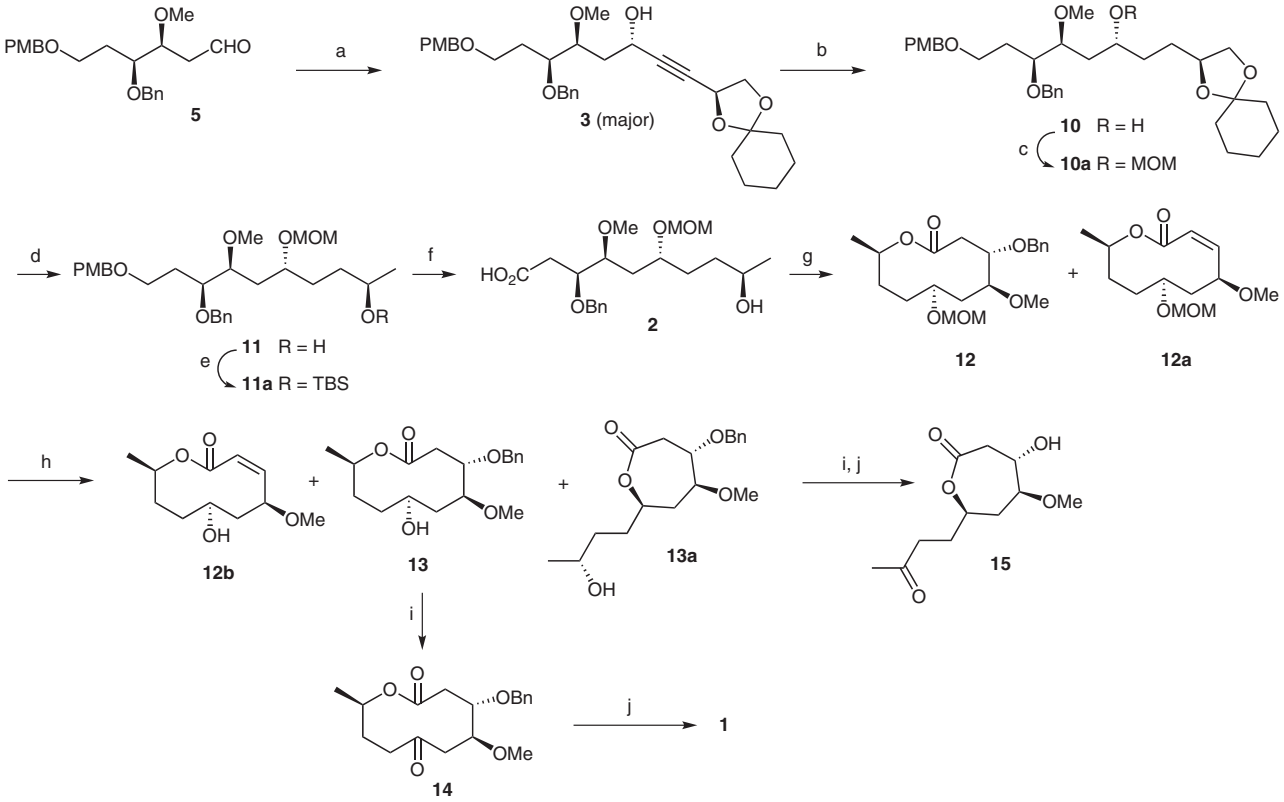


Scheme 2 *Reagents and conditions*: (a) (i) CBr_4, TPP, THF, –10 °C, 30 min, then aldehyde; (ii) EtMgBr, THF, 0 °C to r.t., 30 min, 60% (over two steps); (b) allylSn(Bu)$_3$, $MgBr_2 \cdot 2Et_2O$, CH_2Cl_2, –78 to –20 °C, 95%; (c) NaH, MeI, THF, 0 °C to r.t., 98%; (d) (i) cat. OsO_4, NMO, acetone–H_2O (4:1), 12 h; (ii) $NaIO_4$, CH_2Cl_2, 0 °C to r.t., 6 h, 85% (over two steps).

As envisaged, compound **5** was obtained from L-malic acid (Scheme 2). Thus, L-malic acid was converted into aldehyde **7** according to the modified literature procedure.[5b] The thus prepared aldehyde **7** on chelation-controlled allylation [allylSn(Bu)$_3$, $MgBr_2 \cdot 2Et_2O$, CH_2Cl_2, –78 to –20 °C] afforded highly stereoselective *syn*-diol derivative **8** (95%, de >97%).[7] The absolute stereochemistry of the newly created compound **8** was assigned based on literature and the synthesis continued as envisaged. The terminal olefin in **8** was exploited to generate aldehyde **5** (85%) through the conventional dihydroxylation–oxidative cleavage protocol.

In order to prepare propargyl alcohol **3**, alkyne **4** (Scheme 3) was treated with *n*-BuLi in THF at –78 °C and the resulting acetylenic anion was quenched with aldehyde **5** to furnish **3** (92%, de 60%) as a chromatographically separable diastereomeric mixture.[8] The major diastereomer was taken up for further use so that the ensuing NMR spectra are simplified. Also this particular carbon eventually correlates to C-6 ketone in macrolide **1** and chirality ceases to be of any consequence. Exhaustive reduction of the triple bond in **3** under the standard conditions gave **10** in quantitative yield. Subsequently, the newly generated hydroxy group in **10** was protected (MOMCl, DIPEA, CH_2Cl_2, 0 °C to r.t.) to afford **10a** (90%). Later, the cyclohexylidene group of **10a** was



Scheme 3 *Reagents and conditions*: (a) **4**, *n*-BuLi, THF, –78 °C, 3 h, 92%; (b) PtO_2, H_2, EtOAc, $NaHCO_3$, r.t., 1 h, 100%; (c) DIPEA, MOMCl, CH_2Cl_2, 0 °C to r.t., 12 h, 90%; (d) (i) PTSA, MeOH, r.t., 12 h; (ii) NaH, TsCl, 0 °C to r.t., 2 h; (iii) LAH, THF, 0 °C to r.t., 1 h, 65% (over three steps); (e) TBSCl, imidazole, CH_2Cl_2, r.t., 98%; (f) (i) DDQ, CH_2Cl_2–H_2O (9:1), r.t., 30 min, 95%; (ii) $(COCl)_2$, DMSO, CH_2Cl_2, Et_3N, –78 °C; (iii) $NaClO_2$, $NaH_2PNO_4 \cdot H_2O_2$, *t*-BuOH–2-methyl-2-butene (3:1), 0 °C to r.t., 12 h, 85%; (iv) TBAF, THF, r.t., 24 h, 95%; (g) 2,4,6-trichlorobenzoyl chloride, Et_3N, THF, 0 °C, 3 h, then DMAP, toluene, 110 °C, 8 h, **12** (48%) and **12a** (12%); (h) for conditions see Table 1; (i) DMP, CH_2Cl_2, 0 °C to r.t., 4 h, 95%; (j) Pd/C, H_2, EtOAc, 4 h, r.t., 95%.

deprotected (PTSA, MeOH, r.t.) to afford the corresponding diol, which was selectively monotosylated (TsCl, NaH, r.t.) and exposed to LAH to transform into the methyl group of **11** (65% over three steps). The next task was to protect the secondary OH group as its silyl ether (TBSCl, imidazole, CH_2Cl_2, r.t.) and release the PMB group (DDQ, CH_2Cl_2–H_2O, r.t.) in order to oxidize the ensuing alcohol into an acid.

Accordingly, the primary alcohol was oxidized to the corresponding acid by a two-step process; firstly to an aldehyde by Swern oxidation and then on perchlorite oxidation ($NaClO_2$, $NaH_2PO_4{\cdot}2H_2O$, *t*-BuOH, 2-methyl-2-butene) to afford the seco acid **2** (85% over two steps). Yamaguchi macrolactonization[9] of **2** gave the required macrolide **12** (48%), along with the α,β-unsaturated derivative **12a** (12%) as an inseparable mixture. Hence, macrolide **12** was characterized at a later stage. To continue the synthesis, MOM deprotection (TMSBr, CH_2Cl_2, –5 to 0 °C, entry 10, Table 1)[10] of macrolide mixture **12** and **12a** afforded **13** (68%) and **12b** (17%), respectively, as chromatographically separable compounds. Likewise, compound **13a** was the major product when the deprotection was performed under different reaction conditions (see Table 1). Interestingly, it may be noted that with the right choice of reagent system one can alter the product profile either to **13/12b** or **13a/12b** as separable mixtures. Macrolide **12b** was characterized by its ^{1}H NMR spectrum, which revealed the characteristic olefinic protons at δ = 6.25 as a double doublet (*J* = 11.3, 5.8 Hz), the other one at δ = 5.84 also as a double doublet (*J* = 11.3, 1.8 Hz), and the methyl protons at δ = 1.36 as a doublet (*J* = 6.2 Hz). Further, oxidation of **13** under Dess–Martin periodinane conditions[11] gave **14** (95%), and finally debenzylation (Pd/C, H_2, EtOAc, r.t.) gave the target compound **1** (95%). The synthetic **1** was thoroughly characterized by its spectral data. Its ^{1}H NMR spectrum revealed that the characteristic H-9 at δ = 5.04 as a multiplet, the protons due to OMe appeared at δ = 3.43 as a singlet, and the methyl protons at δ = 1.26 as a doublet (*J* = 6.3 Hz). The MS peak revealed the 231 [M +1]$^+$ ion, $[\alpha]_D^{25}$ +58.0 (*c* 0.12, $CHCl_3$) {natural **1**; $[\alpha]_D^{25}$ +59.0 (*c* 0.017, $CHCl_3$)[1]}. The physical and spectroscopic data of our synthetic sample **1**[1,12] were identical to those of the reported natural product.

In order to obtain a product profile in favor of the required compound, standardization of MOM-deprotection reaction (see Table 1) was felt necessary. As evident from Table 1, most of the times **13a** (85%, Scheme 3) was the major product which was tentatively assigned as **13** but whose structure was clarified in due course of synthesis. Such acid-catalyzed ring contractions or expansions to afford thermodynamically stable compounds is well known in the literature.[13] Subsequently, when the ^{1}H NMR spectrum of **13a** was compared with that of the natural product, there appeared inadequacies especially the ester-linked methine proton appeared at δ = 4.5 as a multiplet instead of at δ = 5.09 for the natural product and the methyl protons at δ = 1.18 as a doublet (*J* = 6.2 Hz). Discounting the differences in NMR values, the rest of the synthesis was continued. Consequently, **13a** upon oxidation and debenzylation as applied earlier afforded **15**. A closer inspection at the spectral data revealed that indeed **15** is not **1**. For instance, ^{1}H NMR spectra of **15** displayed the methyl protons at δ = 2.1 as a singlet, the protons due to OMe appeared at δ = 3.38 as a singlet, and the ester-linked methine proton at δ = 4.57 as a multiplet. The $[\alpha]_D^{25}$ value was –105.3 (*c* 0.15, $CHCl_3$) much different to the reported value.[1] Taking into account all the spectral details, the structure of the macrolide was unambiguously assigned as the heptanolide **15**.[12]

Table 1 Various Reaction Conditions Used for the MOM Deprotection in **12** and **12a**[a]

Entry	Reaction conditions	Time (h)	Yield of **13** (%)	Yield of **13a** (%)	Yield of **12b** (%)
1	PPTS, *t*-BuOH, r.t.	24	n.d.	n.d.	n.d.
2	PPTS, *t*-BuOH, reflux	4	n.d.	68	17
3	PTSA, *t*-BuOH, r.t.	24	n.d.	n.d.	n.d.
4	PTSA, *t*-BuOH, reflux	4	n.d.	65	15
5	TFA, CH_2Cl_2, r.t.	0.5	n.d.	67	16
6	1 N HCl, MeOH, r.t.[b]	0.5	30	10	6
7	1 N HCl, MeOH, r.t.[b]	1	25	25	10
8	1 N HCl, MeOH, r.t.[b]	2	10	45	15
9	1 N HCl, MeOH, r.t.	12	n.d.	65	17
10	TMSBr, CH_2Cl_2, –5 to 0 °C	2	68	n.d.	17

[a] n.d. = not detected.
[b] Starting material recovered.

In conclusion, a stereoselective total synthesis of a novel ten-membered macrolide **1** was accomplished by means of a versatile strategy, wherein L-malic acid and (2*R*)-2,3-*O*-cyclohexylideneglyceraldehyde were used as the inexpensive starting materials for accessing both the advanced intermediates for use in a convergent synthetic strategy. Interestingly, synthesis of two artifacts **12b** and **15**, hitherto unknown, was also reported en route.

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(12) **Spectral Data of Selected Compounds**

Compound **9**: colorless syrup; $[\alpha]_D^{25}$ –37.3 (*c* 2.0, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$): δ = 7.35–7.17 (m, 5 H), 7.13 (d, *J* = 8.4 Hz, 2 H), 6.79 (d, *J* = 8.4 Hz, 2 H), 4.61 (d, *J* = 9.7 Hz, 2 H), 4.55–4.39 (m, 2 H), 4.31 (d, *J* = 7.1 Hz, 2 H), 4.04 (t, *J* = 7.7 Hz, 1 H), 3.86–3.77 (m, 1 H), 3.77 (s, 3 H), 3.67–3.58 (m, 1 H), 3.58–3.41 (m, 2 H), 3.35 (s, 3 H), 3.29–3.02 (m, 1 H), 2.00–1.75 (m, 2 H), 1.75–1.55 (m, 10 H), 1.40–1.30 (m, 2 H). ^{13}C NMR (75 MHz,$CDCl_3$): δ = 159.0, 137.9, 130.4, 129.2, 128.3, 127.9, 127.7, 113.6, 110.8, 86.3, 82.3, 79.6, 75.3, 72.7, 72.4, 69.5, 66.1, 65.1, 61.0, 57.9, 55.1, 37.0, 35.7, 35.3, 29.6, 24.9. FTIR (neat): 3400, 3090, 2910, 2250, 1110 cm^{-1}. ESI-MS: *m/z* = 539 $[M + H]^+$, 556 $[M + NH_4]^+$. Anal. Calcd for $C_{32}H_{42}O_7$: C, 71.35; H, 7.86. Found: C, 71.41; H, 7.79.

Seco acid **2**: colorless liquid; $[\alpha]_D^{25}$ –3.8 (*c* 3.0, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$): δ = 7.28 (m, 5 H), 4.72–4.49 (m, 4 H), 4.15–4.05 (m, 1 H), 3.82–3.69 (m, 1 H), 3.69–3.60 (m, 1 H), 3.43–3.25 (m, 7 H), 2.66 (dd, *J* = 15.8, 4.1 Hz, 1 H), 2.51 (dd, *J* = 15.8, 7.9 Hz, 1 H), 1.87–1.71 (m, 1 H), 1.66–1.38 (m, 5 H), 1.16 (d, *J* = 6.0 Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 175.7, 138.5, 128.2, 127.9, 127.5, 96.1, 78.2, 74.9, 72.4, 67.7, 58.9, 57.7, 55.5, 34.4, 33.6, 30.0, 24.1, 19.7. FTIR (neat): 3500, 3150, 2930, 1690, 1120 cm^{-1}. ESI-MS: *m/z* = 385 $[M + H]^+$, 407 $[M + Na]^+$. Anal. Calcd for $C_{20}H_{32}O_7$: C, 62.48; H, 8.39. Found: C, 62.61; H, 8.31.

Compound **12b**: colorless syrup; $[\alpha]_D^{25}$ –63.3 (*c* 0.35, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$): δ = 6.25 (dd, *J* = 11.3, 5.8 Hz, 1 H), 5.84 (dd, *J* = 11.3, 1.8 Hz, 1 H), 4.66–4.52 (m, 1 H), 4.13–3.95 (m, 1 H), 3.77 (t, *J* = 6.9 Hz, 1 H), 3.25 (s, 3 H), 2.34–1.53 (m, 6 H), 1.36 (d, *J* = 6.2 Hz, 3 H). ESI-MS: *m/z* = 225 $[M + Na]^+$. Anal. Calcd for $C_{11}H_{18}O_4$: C, 61.66; H, 8.47. Found: C, 61.53; H, 8.59.

Compound **13a**: colorless syrup; $[\alpha]_D^{25}$ +8.33 (*c* 0.45, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$): δ = 7.29 (m, 5 H), 4.81 (d, *J* = 11.7 Hz, 2 H), 4.67–4.53 (m, 2 H), 4.45 (d, *J* = 11.7, 1 H), 3.89–3.72 (m, 1 H), 3.46 (m, 1 H), 3.31 (s, 3 H), 3.09 (d, *J* = 13.5 Hz, 1 H), 2.93 (dd, *J* = 14.2, 6.6 Hz, 1 H), 2.34–1.69 (m, 2 H), 1.63–1.42 (m, 4 H), 1.18 (d, *J* = 6.2 Hz, 3 H). ESI-MS: *m/z* = 345 $[M + Na]^+$. Anal. Calcd for $C_{18}H_{26}O_7$: C, 67.06; H, 8.13. Found: C, 67.21; H, 8.02

Compound **14**: colorless syrup; $[\alpha]_D^{25}$ +10.7 (*c* 0.55, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$): δ = 7.46–7.29 (m, 5 H), 5.18–4.98 (m, 1 H), 4.82 (d, *J* = 11.3 Hz, 1 H), 4.59 (d, *J* = 11.3 Hz, 1 H), 4.11 (ddd, *J* = 11.7, 8.4, 3.6 Hz, 1 H), 3.56 (s, 3 H), 3.46–3.34 (m, 1 H), 2.95–2.59 (m, 3 H), 2.53–2.12 (m, 4 H), 2.05–1.90 (m, 1 H) 1.32 (d, *J* = 6.6 Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 208.2, 169.2, 132.9. 129.5, 128.3, 127.6, 81.9, 79.6, 72.1, 71.3, 58.9, 43.9, 40.2, 39.6, 33.2, 19.7. FTIR (neat): 3452, 1733, 1726 cm^{-1}. HRMS: *m/z* calcd for $C_{18}H_{24}O_5NaCl$ $[M + Na]^+$: 343.1521; found: 343.1512.

Compound **1**: colorless syrup; $[\alpha]_D^{25}$ +58.0 (*c* 0.12, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ = 5.04 (m, 1 H), 4.11 (ddd, *J* = 11.6, 8.7, 2.9 Hz, 1 H), 3.43 (s, 3 H), 3.35 (ddd, *J* = 10.2, 8.2, 2.4 Hz, 1 H), 3.09 (br s, 1 H, OH), 2.93 (dd, *J* = 17.4, 7.7 Hz, 1 H), 2.86 (dd, *J* = 17.4, 3.4 Hz, 1 H), 2.63 (dd, *J* = 17.4, 2.9 Hz, 1 H), 2.45 (dd, *J* = 17.4, 2.4 Hz, 1 H), 2.41 (ddd, *J* = 13.6, 7.2. 3.8 Hz, 1 H), 2.32 (ddd, *J* = 14.0, 10.6, 3.4 Hz, 1 H), 2.11 (m, 1 H), 2.02 (m, 1 H), 1.26 (d, *J* = 6.3 Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 208.6, 169.2, 81.9, 71.6, 68.3, 57.3, 41.7, 40.4, 39.7, 33.1, 19.6. FTIR (neat): 3458, 1735, 1726 cm^{-1}. HRMS: *m/z* calcd for $C_{11}H_{18}O_5NaCl$ $[M + Na]^+$: 253.1051; found: 253.1048.

Compound **15**: colorless syrup; $[\alpha]_D^{25}$ –105.3 (*c* 0.15, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$): δ = 4.57 (m, 1 H), 4.11–4.06 (m, 1 H), 3.47 (m, 1 H), 3.38 (s, 3 H), 3.18 (d, *J* = 14.1 Hz, 1 H), 2.79–2.55 (m, 3 H), 2.14 (s, 3 H), 2.04 (dd, *J* = 9.1, 2.0 Hz, 1 H), 1.96–1.78 (m, 3 H). FTIR (neat): 3442, 1734, 1728 cm^{-1}. ESI-MS: *m/z* = 231 $[M + H]^+$. Anal. Calcd for $C_{11}H_{18}O_5$: C, 57.38; H, 7.88. Found: C, 57.51; H, 7.76.

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