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Graphical Abstract

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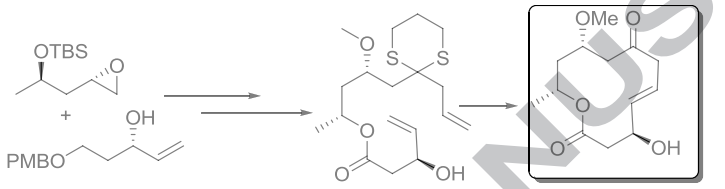

Dendrodolide A (**1**)

Pergamon

TETRAHEDRON LETTERS

The first stereoselective synthesis of dendrodolide A

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Abstract: The first stereoselective total synthesis of natural product, dendrodolide A (**1**) is described from readily available (*R*)-propylene oxide and 3-buten-1-ol as starting materials. The synthesis was achieved in 10 steps with an overall yield of 19.1%. The key steps involved in the synthesis are Jacobsen hydrolytic kinetic resolution, epoxide ring opening with 2-allyl-1, 3-dithiane, Yamaguchi esterification and ring-closing metathesis (RCM).

Keywords: Jacobsen hydrolytic kinetic resolution / Epoxides / Yamaguchi esterification/ Ring-closing metathesis / Asymmetric synthesis / Macrolides

Marine microorganisms have been proven to be a rich repertoire of innumerable secondary metabolites with novel structures and wide-ranging biologically properties, particularly, half of them were from fungal genera.[1] Recently, fungal metabolites, dendrodolides A-D,[2] (Fig.1) were isolated from the fungus *Dendrodochium sp.*, (a fungus associated with the sea cucumber *Holothuria nobilis* Selenka) by Wen Zhan and co-workers. The gross structure of **1** was established by means of detailed spectroscopic analysis (1D, 2D NMR and Mass) and X-ray single-crystal diffraction studies. It was further shown that dendrodolide A (**1)** exhibited *in vitro* cytotoxicity against the tumor cell line SMMC-7721with IC_{50} value of 19.2 µg/mL. Structurally, dendrodolide A (**1**) is a 12-membered macrolactone, featuring a *trans* double bond, one hydroxyl group, and methoxy group moieties. Because of their important biological properties coupled with the presence of interesting unique stereogenic variations, as well as the limited amounts available from natural sources, dendrodolides have attracted the attention of a number of synthetic organic chemists towards their synthesis worldwide. However, till date there are no reports on the synthesis of **1**. These facts coupled with the interesting structural feature of dendrodolide A (**1**) prompted us to undertake the synthetic study. In continuation of our interest in targeting lactone-containing molecules[3] for total synthesis, herein we describe the stereoselective total synthesis of dendrodolide A (**1**).

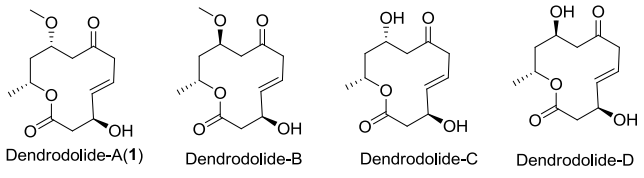

Figure 1.Structures of dendrodolides (A-D)

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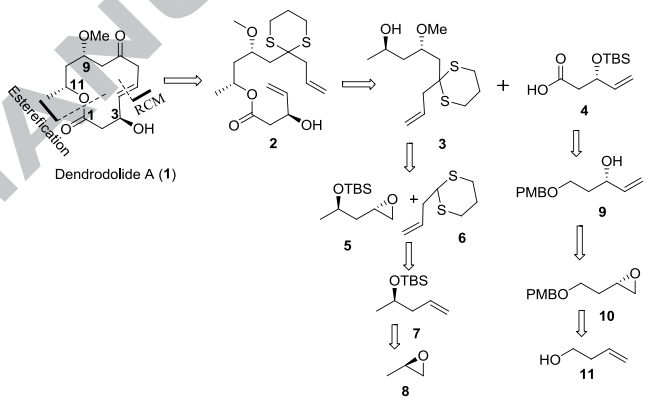
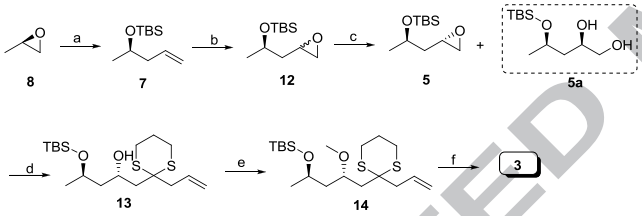


Scheme 1: Retrosynthetic analysis of dendrodolide A (**1**)

Recognizing the importance of developing an efficient synthetic strategy for **1**, our synthetic approach to a 12-membered macrolide, dendrodolide involves a RCM reaction (Scheme 1). Thus, disconnection of the C-C double bond revealed the bis terminal olefin **2** as a potential key intermediate. A subsequent disconnection of **2** through Yamaguchi esterification converts it into fragments **3** and **4**. The alcohol fragment **3** envisaged by regioselective ring opening of epoxide **5** with 2-allyl-1,3-dithiane **6**, the epoxide **5** could, in turn be accessed from opening of (*R*)-propylene oxide **8** with vinyl magnesium bromide through epoxidation followed by Jacobsen hydrolytic kinetic resolution. On the other hand, acid fragment **4** could be obtained by stepwise transformations from commercially available 3-buten-1-ol (**11**) through epoxidation and Jacobsen resolution reactions. Thus, our present total synthesis will be highlighted by utilization of Jacobsen hydrolytic kinetic resolution which directs the construction of the stereocentre at C-3, C-9, C-11 and Grubb's ring closing metathesis for the formation of 12-membered lactone ring. Furthermore, the simplicity of the precursors of this route makes it attractive for the library synthesis of

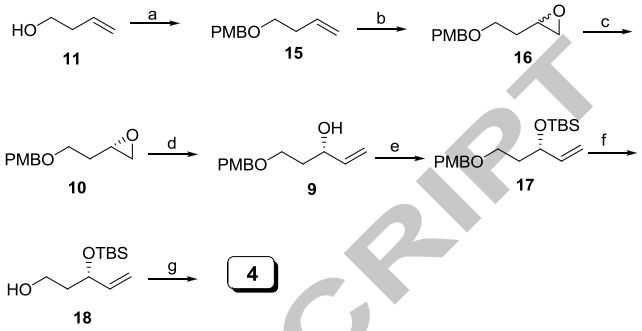
the dendrodolides for the biological screening, as extensive biological screening was not done due to the limited amounts from natural source.

For an enantioselective approach for the synthesis of **5**, we selected (*R*)-propylene oxide **8** as a chiral synthon, readily prepared from racemic-propylene oxide through Jacobsen hydrolytic kinetic resolution[4] (HKR) using (*R, R*)-(salen)-Co^{III} OAc. Thus, treatment of (*R*)-propylene oxide **8** with vinyl magnesium bromide in the presence of CuI afforded homoallylic alcohol[5,6] in 89% yield, in which the secondary hydroxyl group was protected as its TBS ether using TBSCl, imidazole, in DCM to give **7** in 98% yield. Epoxidation of **7** with *m*-CPBA afforded a mixture of two diastereomers **12** (*anti:syn*/3:1), which was then subjected to Jacobsen hydrolytic kinetic resolution (HKR) method with (*S, S*)-(salen)-Co^{III} ·OAc complex (0.5 mol %) and water (0.55 equiv) in THF (0.55 equiv) to afford the diastereomerically pure epoxide **5**[6] in 70% yield (>94% ee) (determined by chiral HPLC) and diol **5a** in 21% yield. Ring opening of epoxide **5** with 2-allyl-1,3-dithiane[7] yielded compound **13**[8] in 87% yield. Subsequent methylation of alcohol **13** using MeI/NaH [9] afforded **14** in 98% yield. Removal of TBS group with TBAF furnished the required alcohol **3**[10] in 96% yield.



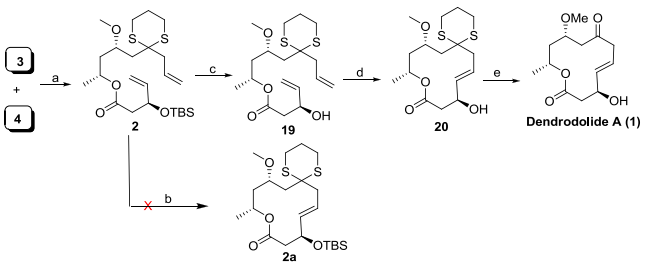
Scheme2. Reagents and conditions: (a) (i) vinyl magnesium bromide, CuI, THF, -78°C to -20 °C, 12 h, 89%; (ii) TBDMSCl, imidazole, CH_2Cl_2, 0 °C to rt, 4 h, 98%; (b) *m*-CPBA, CH_2Cl_2, 0 °C to rt, 12 h, 92%, (c) (*S,S*)-(salen)-Co^{III}· OAc (0.5 mol %), H_2O (0.55 equiv.), THF, 0°C to rt, 18 h, 45% for **5**, 47% for **5a**; (d) **6**, *n*-BuLi, dry THF,–78 °C to –20 °C, 2 h, 87%; (e) NaH, MeI, THF, 0 °C to rt, 5 h, 98%; (f) TBAF, THF, 0°C to rt, 4 h, 96%.

The journey for the synthesis of acid fragment **4** began from readily available 3-buten-1-ol (**11)** (Scheme 3), which was protected as PMB ether using PMBBr, NaH and a catalytic amount of TBAI in DMF to afford **15**[11] in 96% yield. The compound **15** was subjected to m-CPBA epoxidation to give racemic epoxide **16**[12], which was subjected to Jacobsen's hydrolytic kinetic resolution using the (*S, S*)-catalyst to give optically pure epoxide (S)-**10**[13] in 44% yield (determined by chiral HPLC). The regioselective ring opening of epoxide[14] **10** with dimethylsulfonium methylide ($Me_3S^+I^-$), *n*-BuLi, in THF afforded the allylic alcohol **9** in 92% yield. The allylic alcohol was subsequently protected with TBSCl and imidazole in DCM to afford **17**[5] in 96% yield. Finally deprotection of PMB group with DDQ[15] followed by oxidation with TEMPO/BAIB in CH_2Cl_2:H_2O (1:1) afforded acid **4**[16] in 92% yield.



Scheme 3. Reagents and conditions: (a) PMBBr, NaH, DMF, 0 °C to rt, 12 h, 96%; (b) *m*-CPBA, CH_2Cl_2, 0 °C to rt, 12 h, 89%; (c) (*S,S*)-(salen)-Co^{III}·OAc (0.5 mol%), H_2O (0.55 equiv.), 0 °C to rt, 18 h, 45% for 10, 47% for 10a; (d) $Me_3S^+I^-$, n-BuLi, THF, −20 °C, 4 h, 92%; (e) TBSCl, imidazole, DCM, 0°C to rt, 96%; (f) DDQ, CH_2Cl_2 : P^H 7 buffer (9 : 1), 0 °C to rt, 1 h, 92%; (g) TEMPO, BAIB, CH_2Cl_2 : H_2O (1 : 1), 0 °C to rt, 2 h, 92%.

With the two fragments **3** and **4** in our hand, the synthesis proceeded as shown in Scheme 4. The connection between the fragments **3** and **4** was performed using the Yamaguchi protocol[17] (2,4,6-trichlorobenzoyl chloride, Et_3N, THF, DMAP, toluene), which yielded key olefin **2** in good yield. Having the key intermediate **2** in hand, we next planned for ring-closing metathesis (RCM) reaction of **2** with the Grubbs second generation catalyst (G-II, 25 mol %). However, the reaction did not progress[18] and the starting material was completely recovered. At this stage, we investigated the alternative strategy, viz., deprotection followed by the RCM reaction to achieve the compound **20**. Thus, deprotection of TBS group using TBAF gave **19**[10] with 96% yield, which was then subjected to the RCM reaction using G-II (25 mol %) in dry DCM (deoxygenated), which at reflux temperature gratifyingly yielded macrolide **20**[19] in 65% yield and with good E-selectivity (>95%).



Scheme 4. Reagents and conditions: (a) **4**, 2,4,6-trichlorobenzoylchloride, Et_3N, THF, 0 °C to rt, 2 h, then **3**, DMAP, toluene, 0 °C, 2 h, 98%; (b) G-II (25 mol%), CH_2Cl_2, reflux, 20 h, (c) TBAF, THF, 0°C to rt, 4 h, 96%; (d) G-II (25 mol%), CH_2Cl_2, reflux, 20 h, 65%; (e) $CaCO_3$, I_2, THF:H_2O (4:1), 0 °C, 20 min, 92%.

Finally, removal of 1,3-dithiane group[20] in **20** with $CaCO_3$, I_2, in THF: H_2O (4:1) furnished the presumed, dendrodolide A (**1**) with 92% yield. All the intermediate compounds including the dendrodolide A (**1**) were fully characterized [21] by ^1H NMR, ^{13}C NMR, and Mass spectral data. The spectral and analytical data of synthetic dendrodolide A (**1**) were in agreement with the reported natural dendrodolide data.

In conclusion, we have accomplished the first total synthesis of dendrodolide A (**1**) in 10 steps with an overall yield of 19.1 % , featuring the Jacobsen catalyst hydrolytic kinetic resolution (HKR), Yamaguchi esterification and ring-closing metathesis reactions (RCM) as a key reactions. Following the same series of reactions, we are presently investigating the synthesis of other dendrodolide including their analogues. Its biological properties will also be investigated and compared with those of the natural product.

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21. Spectroscopic data for representative examples:

Compound **13**: Colorless oil; $[\alpha]_D^{25}$= -3.36 (*c* = 1.6, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.96-5.86 (m, 1 H), 5.18-5.17 (m, 1 H), 5.16-5.14 (m, 1 H), 4.28-4.22 (m, 1 H), 4.15-4.09 (m, 1 H), 3.59-3.56 (bs, 1 H), 3.0-2.96 (m, 1 H), 2.91-2.76 (m, 4 H), 2.73-2.67 (m, 1 H), 2.28-2.21 (m, 1 H), 2.05-1.98 (m, 1 H), 1.97-1.91 (m, 1 H), 1.89, 1.86 (d, *J* = 1.8 Hz, 1 H), 1.64-1.58 (m. 1 H), 1.45-1.39 (m, 1 H), 1.18 (d, *J* = 6.2 Hz, 3 H), 0.9 (s, 9 H), 0.1 (s, 3 H), 0.08 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 132.5, 118.8, 65.7, 65.0, 51.5, 46.6, 45.3, 43.9, 26.3, 26.0, 25.8 (3 C), 24.8, 23.8, 17.9, -4.4, -4.9; IR (KBr): $\tilde{\nu}$ = 3478, 2956, 1741, 1649, 1255, 836 cm^{-1}; MS (ESI): m/z = 399 $[M + Na]^+$.

Compound 14: Colorless liquid; $[\alpha]_D^{25}$= -8.22 (*c* = 0.45, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.99-5.87 (m, 1 H), 5.18-5.16 (bs, 1 H), 5.15-5.12 (m, 1 H), 3.99-3.91 (m, 1 H), 3.72-3.65 (m, 1 H), 3.35 (s, 3 H), 2.90-2.68 (m, 6 H), 2.15, 2.12 (d, *J* = 5.8 Hz, 1 H), 1.98-1.87 (m, 3 H), 1.71-1.59 (m, 2 H), 1.17 (d, *J* = 6.1 Hz, 3 H), 0.9 (s, 9 H); 0.09 (s, 3 H), 0.08 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 113.3, 118.2, 74.9, 65.5, 56.0, 51.5, 46.5, 43.6, 43.3, 26.19, 26.16, 25.9 (3 C), 24.9, 24.3, 18.0, -3.9, -4.6; IR (KBr): υ_{max} = 2959, 2855, 1742, 1260, 802, 773 cm^{-1}; MS (ESI): m/z = 413 $[M + Na]^+$.

Compound 3: Colorless liquid; $[\alpha]_D^{25}$= -12.7 (*c* = 0.85, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.98-5.87 (m, 1 H), 5.18-5.11 (m, 2 H), 4.17-4.10 (m, 1 H), 3.85-3.8 (m, 1 H), 3.39 (s, 3 H),2.91-2.68 (m, 6 H), 2.25 (dd, *J* = 15.2, 7.0 Hz, 1 H), 2.1 (dd, *J* = 15.4, 3.0 Hz, 1 H), 1.98- 1.89 (m, 3 H), 1.51, 1.48 (q, *J* = 4.4, 2.4 Hz, 1 H), 1.2 (d, *J* = 6.1 Hz, 3 H); (^{13}C NMR (75 MHz, $CDCl_3$): δ = 133.1, 118.5, 77.3, 65.1, 56.4, 51.7, 43.6, 42.8, 41.4, 26.1, 26.0, 24.9, 23.7; IR (KBr): υ_{max} = 3429, 2927, 1643, 1219, 772 cm^{-1}; HRMS (ESI): calcd. for $C_{13}H_{24}NaO_2S_2$ $[M + Na]^+$ 299.1110; found 299.1106.

Compound 4: Colorless oil; $[\alpha]_D^{25}$= +3.73 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.86 (ddd, *J* = 16.8, 10.3, 6.2 Hz, 1 H), 5.26 (dt, *J* = 17.0, 1.3 Hz, 1 H), 5.12, 5.11 (dt, *J* = 10.3, 1.2 Hz, 1 H), 4.58 (q, *J* = 6.7 Hz, 1 H), 2.56 (dd, *J* = 6.8, 4.4 Hz, 2 H), 0.89 (s, 9 H); 0.08 (s, 3 H), 0.07 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 176.8, 139.6, 115.1, 70.5, 43.2, 25.6 (3 C), 18.0, -4.4, -5.2; IR (KBr): υ_{max} = 2928, 2876, 1716, 1460, 1092, 773 cm^{-1}; MS (ESI): m/z = 253 $[M + Na]^+$.

Compound 2: Colorless liquid; $[\alpha]_D^{25}$= -1.3 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.98-5.83 (m, 2 H), 5.27-5.22 (m, 1 H), 5.18-5.16 (bs, 1 H), 5.15-5.12 (m, 1 H), 5.1-5.06 (m, 1 H), 5.04-4.98 (m, 1 H), 4.59 (q, *J* = 13.1, 6.2 Hz, 1 H), 3.58-3.52 (m, 1 H), 3.32 (s, 3 H), 2.90-2.81 (m, 3 H), 2.79, 2.68 (m, 3 H), 2.56 (dd, *J* = 14.8, 7.0 Hz, 1 H), 2.46 (dd, *J* = 14.8, 6.2 Hz, 1 H), 2.1 (dd, *J* = 15.4, 6.4 Hz, 1 H), 2.0-1.93 (m, 2 H), 1.89-1.82 (m, 1 H), 1.73-1.66 (m, 2 H), 1.26 (d, *J* = 6.2 Hz, 3 H) 0.88 (s, 9 H); 0.07 (s, 3 H), 0.05 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.3, 140.2, 133.2, 118.3, 114.6, 75.1, 70.5, 68.5, 56.7, 51.3, 44.0, 43.8, 43.5, 42.2, 26.15, 26.11, 25.7 (3 C), 24.9, 20.5, 18.1, -4.4, -4.9; IR (KBr): υ_{max} = 2929, 1733, 1219, 802, 772 cm^{-1}; HRMS (ESI): calcd. for $C_{24}H_{44}NaO_4S_2Si$ $[M + Na]^+$ 511.2342; found 511.2381.

Compound 19: Colorless oil; $[\alpha]_D^{25}$= -8.6 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.96-5.86 (m, 2 H), 5.35-5.32 (t, *J* = 1.5, Hz, 1 H), 5.18-5.15 (m, 3 H), 5.14-5.12 (m, 1 H), 4.58-4.54 (m, 1 H), 3.6-3.55 (m, 1 H) 3.33 (s, 3 H), 3.14-3.1 (bs, 1 H, OH), 2.93- 2.85 (m, 2 H), 2.82-2.69 (m, 5 H), 2.63-2.57 (m, 1 H), 2.56-2.5 (m, 1 H), 2.11 (dd, *J* = 15.4, 6.0 Hz, 1 H), 1.99-1.91 (m, 3 H), 1.72-1.65 (m, 1 H), 1.25 (d, *J* = 6.2 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.6, 138.8, 133.2, 118.4, 115.2, 75.0, 68.8 (2 C), 56.7, 51.3, 43.8, 43.5, 41.6, 42.2, 26.12, 26.09, 24.8, 20.6; IR (KBr): υ_{max} = 2959, 2919, 2851, 1728, 1219, 802, 772 cm^{-1}; HRMS (ESI): calcd. for $C_{18}H_{30}NaO_4S_2$ $[M + Na]^+$ 397.1478; found 397.1514.

Compound 20: Light brown oil; $[\alpha]_D^{25}$= -12.36 (*c* = 0.55, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.89-5.81 (m, 1 H), 5.62-5.56 (m, 1 H), 5.22-5.15 (m, 1 H), 4.57-4.51 (m, 1 H), 3.51-3.44 (m, 1 H) 3.33 (s, 3 H), 2.98- 2.89 (m, 3 H), 2.80-2.70 (m, 3 H), 2.65-2.63 (m, 2 H), 2.12-2.01 (m, 2 H), 1.99-1.84 (m, 3 H), 1.69-1.63 (m, 1 H), 1.24 (d, *J* = 6.2 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.6, 134.9, 127.3, 76.1, 70.0, 68.9, 56.5, 50.7, 45.2, 42.3, 41.8, 41.3, 26.4 (2 C), 25.1, 21.1; IR (KBr): υ_{max} = 3432, 2980, 2911, 2829, 1721, 1276,

1166, 802, 764 cm^{-1}; HRMS (ESI): calcd. for $C_{16}H_{16}NaO_4S_2$ $[M + Na]^+$ 369.1165; found 369.1198.

Compound 1: Colorless crystal; M.P 114-116^{0}C; $[\alpha]_D^{25}$= + 40.4 (*c* = 0.3, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.73-5.71 (m, 2 H), 5.31-5.24 (m, 1 H), 4.58-4.52 (m, 1 H), 3.68-3.63 (m, 1 H) 3.38 (s, 3 H), 3.27 (dd, *J* = 13.6, 6.9 Hz, 1 H), 3.1 (dd, *J* = 13.7, 3.9 Hz, 1 H), 2.87 (dd, *J* = 12.8, 5.3 Hz, 1 H), 2.75 (dd, *J* = 14.0, 4.1 Hz, 1 H), 2.64 (dd, *J* = 13.9, 7.1 Hz, 1 H), 2.47 (dd, *J* = 12.8, 8.5 Hz, 1 H), 1.61-1.57 (m, 2 H), 1.23 (d, *J* = 6.2 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 206.05, 170.9, 136.7, 124.4, 74.8, 69.3, 68.5, 56.87, 49.06, 47.3, 41.57, 41.0, 20.89; IR (KBr): υ_{max} = 3426, 2961, 2851, 2920, 1736, 1261, 1219, 1092, 772 cm^{-1}; HRMS (ESI): calcd. for $C_{13}H_{20}NaO_5$ $[M + Na]^+$ 279.1203; found 279.1198.