Tetrahedron Letters 53 (2012) 1258–1260

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

First stereoselective total synthesis of pectinolide H

D. Ramesh, V. Shekhar, D. Chantibabu, S. Rajaram, U. Ramulu, Y. Venkateswarlu *

Division of Natural Product Chemistry, Indian Institute of Chemical Technology, Hyderabad 500 007, India

ARTICLE INFO

Article history:
Received 21 November 2011
Revised 27 December 2011
Accepted 28 December 2011
Available online 5 January 2012

Keywords:
Asymmetric reduction
Sonogashira coupling
Sharpless dihydroxylation
Still–Gennari olefination
γ-Lactones

ABSTRACT

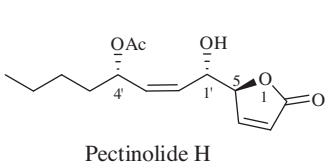
The stereoselective total synthesis of bio-active pectinolide H (**1**) is described. Midland's asymmetric reduction, Sharpless dihydroxylation reactions are involved in generating the stereogenic centers at C-4′, C-5 and C-1′. Other key steps in the synthesis are Sonogashira cross coupling, *Z*-selective Still–Gennari olefination, one-pot acetonide deprotection–lactonization, and Lindlar's reaction. This offers a distinctive strategy for the synthesis of γ-lactones.

Five membered lactone having a substitution at the γ-position is an important structural subunit in many bio-active compounds.[1] γ-Lactone containing natural products are known to exhibit various biological activities,[2] including anti-fungal, anti-bacterial,[3] anti tumor,[4] cytotoxic,[5] cyclooxygenase, or phospholipase A_2 inihibition.[6] Pectinolide H (**1**), a structurally distinctive γ-lactone having three stereogenic centers has been isolated from the chloroform extract of the aerial parts of a Mexican terrestrial plant *Hyptis pectinata*,[7] which is used in traditional Mexican medicine for a multipurpose remedies in the treatment of skin infections, fevers, gastric disturbances,[8] and lung congestion.[9] Pectinolides A–C (**2–4**; Fig. 1) are also isolated from the same plant and known to show cytotoxic and antimicrobial properties.[10] In particular, pectinolide H (**1**) displayed significant antimicrobial activity against a panel of multidrug-resistant strains of *Staphylococcus aureus*.[7] The structure and stereo chemistry of **1** were established on the basis of spectral, chiroptical data, and chemical evidence.

In continuation of our interest in the total synthesis of bio-active natural products,[11] the significant biological properties and important structural features of **1** prompted us to explore the synthesis of this molecule. To the best of our knowledge, there is no report on the synthesis of **1**. Herein, we describe a simple and efficient approach for the stereoselective total synthesis of **1**.

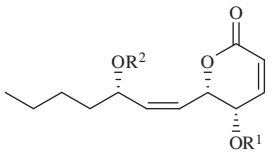
The retro synthetic analysis of **1** is depicted in Scheme 1. The target molecule **1** can be easily envisaged from the *cis* olefinic ester (**5**) by one pot acetonide deprotection and lactonization followed by Lindlar's reaction. The intermediate **5** in turn can be obtained from the *Z*-selective Still–Gennari olefination and other sequential reactions of diol (**6**). The compound **6** was prepared from the Sonogashira cross coupling of alkyne (**7**) and iodoallylic alcohol (**17**). Further, compound **7** was prepared from the acetylenic ketone (**8**) by stereoselective asymmetric reduction (Scheme 1).

As outlined in Scheme 2, the synthesis of **1** commenced from the acetylenic ketone (**8**)[12] and the first stereogenic center was generated by the enantioselective reduction of **8** with (*S*)-alpine borane (**18**) and provided the chiral propargyl alcohol (**9**) in a 75% yield (enantiomeric ratio *S:R* = 87:13).[13] The alcohol (**9**) was protected as corresponding TBS ether (**7**).[12b] Thus obtained compound (**7**) was subjected to Sonogashira cross coupling with (**17**)[14,15a] in the presence of $[Pd(PPh_3)_4]$, CuI to afford allylic alcohol (**10**)[15] in an 88% yield. The primary alcohol in **10** was protected with *p*-methoxybenzyl chloride using NaH in dry THF to afford compound **11** in a 93% yield. Sharpless dihydroxylation of (**11**) with AD-mix-α at 0 °C furnished diol (**6**)[16] in an 82% yield (de 96%), which was protected with 2,2-dimethoxy propane in the presence of a catalytic amount of PTSA to yield compound (**12**)



Pectinolide H

1

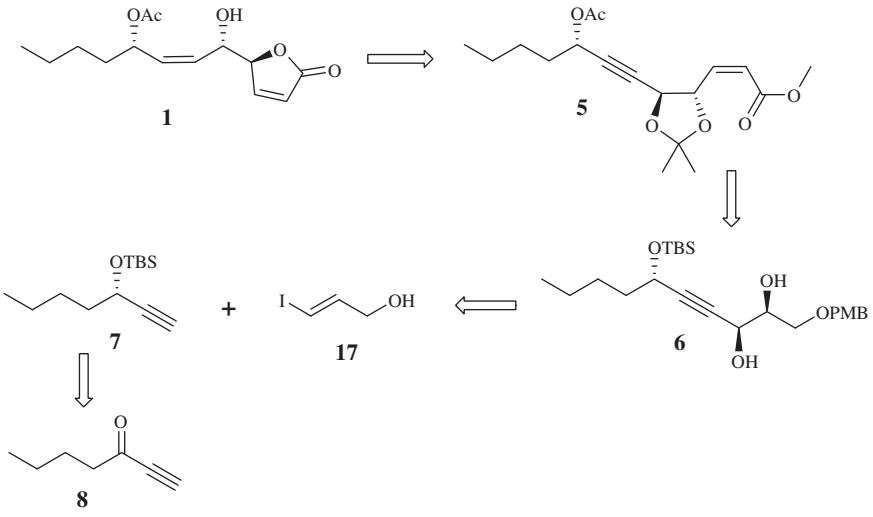


Pectinolide A; $R^1=R^2$=Ac **2**
Pectinolide B; R^1=Ac, R^2=H **3**
Pectinolide C; R^1=H, R^2=Ac **4**

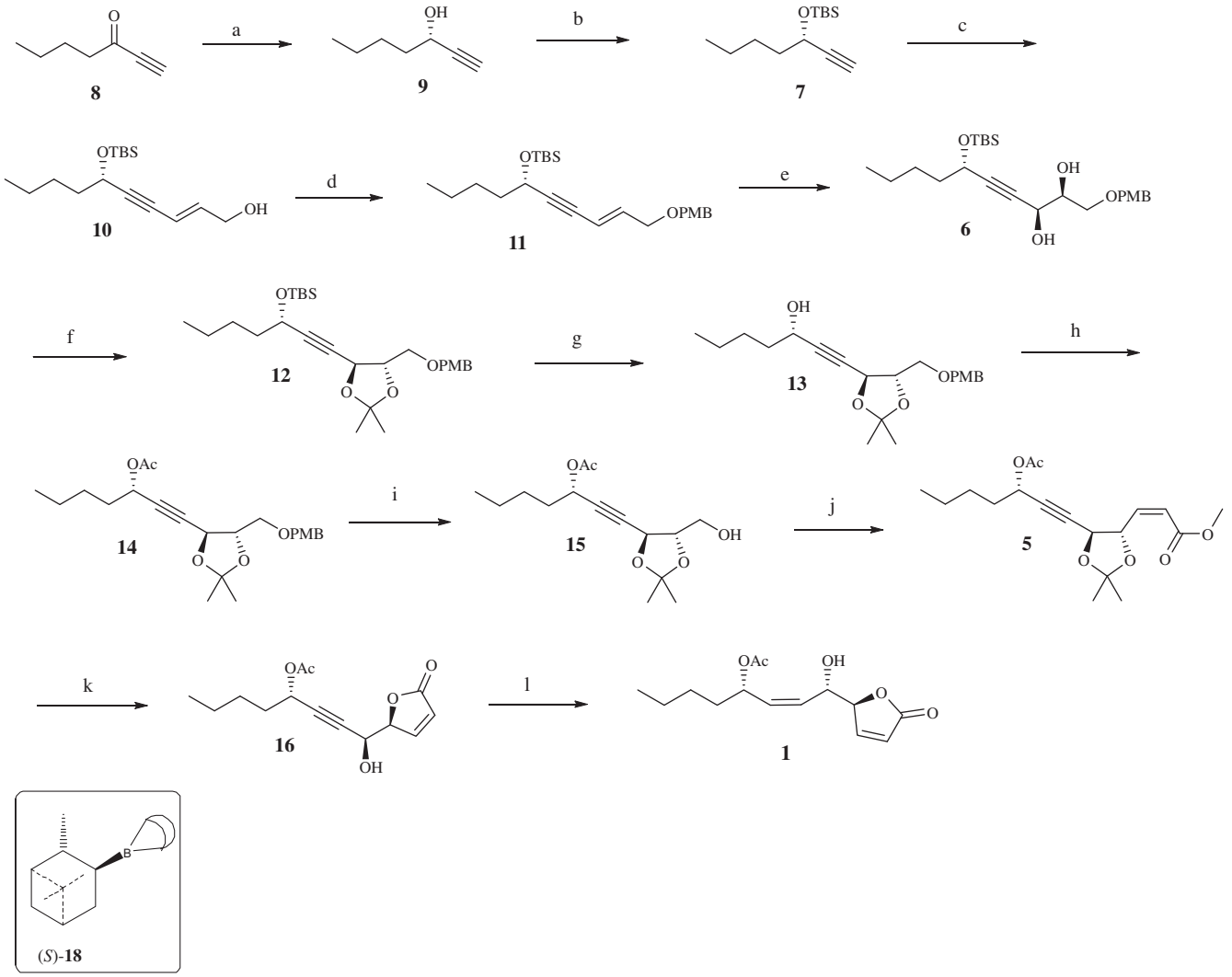
Figure 1. Structures of pectinolides H and A–C.

* Corresponding author. Tel.: +91 40 27193167; fax: +91 40 27160512.
E-mail address: luchem@iict.res.in (Y. Venkateswarlu).

0040-4039/$ - see front matter © 2012 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2011.12.122



Scheme 1. Retrosynthetic analysis of pectinolide H.



Scheme 2. Reagents and conditions: (a) (*S*)-**18**, THF, 8 h, rt, 75%; (b) imidazole, TBDMSCl, DCM, rt, 3 h; (c) **17**, iPr_2NH, $Pd(PPh_3)_4$, CuI, dry benzene, rt, 2 h, 88%; (d) NaH, PMBCl, dry THF, 0 °C to rt, 4 h, 93%; (e) AD-mix-α, $MeSO_2NH_2$, *t*-BuOH/H_2O (1:1), 0 °C, 24 h, 82%; (f) 2,2-dimethoxypropane, PTSA, dry DCM, rt, 12 h, 90%; (g) TBAF, THF, rt, 2 h, 97%; (h) Ac_2O, pyridine, rt, 4 h, 96%; (i) DDQ, DCM/H_2O (10:1), rt, 2 h, 95%; (j) (1) Dess–Martin periodinane, DCM, 0 °C to rt, 2 h, 94%; (2) $(F_3CCH_2O)_2POCH_2COOMe$, 18-crown ether, KHMDS, dry THF, −78 °C, 4 h, 86%; (k) 80% AcOH, 0 °C to rt, 20 h, 96%; (l) Lindlar's catalyst, quinoline, ethyl acetate, rt, 2 h, 88%.

with a 90% yield. The *tert*-butyldimethylsilyl ether group in (**12**) was removed using TBAF in THF to give secondary alcohol (**13**) in a 97% yield, which was acetylated using acetic anhydride in pyridine to afford compound **14** in a 96% yield. The *p*-methoxybenzyl group in **14** was removed employing DDQ in DCM/H_2O (10:1) to give primary alcohol **15** in a 95% yield. The alcohol (**15**) was oxidized with Dess–Martin periodinane (DMP) in DCM to afford aldehyde, which was further subjected to *Z*-selective Still–Gennari olefination[17] by employing bis((2,2,2-trifluoroethyl)(methoxycarbonylmethyl phosphonate)), 18-crown ether, KHMDS in THF to afford *cis*-olefinic ester (**5**) in an 86% yield. Deprotection of acetonide group and lactonization were achieved in one pot using 80% AcOH to give acetylenic lactone (**16**) with a 96% yield. Finally, partial hydrogenation of triple bond in compound **16** over Lindlar's catalyst furnished the target natural product, pectinolide H (**1**) in an 88% yield (Scheme 2). The spectral data[18] and optical rotation {$[\alpha]_D^{25}$ −43.7 (*c* 0.18, $CHCl_3$)} of synthetic pectinolide H (**1**) were in good agreement with the reported data of the natural product.[7]

In conclusion we have reported a simple and efficient approach for the total synthesis of pectinolide H (**1**) in a stereoselective manner. This protocol involves the use of enantioselective Midland's asymmetric reduction, Sonogashira cross coupling, Sharpless dihydroxylation, *Z*-selective Still–Gennari olefination, one pot acetonide deprotection–lactonization, and Lindlar's reaction as key steps.

Acknowledgments

The authors DR, VS, DCB, SR and UR are thankful to CSIR, New Delhi, for the financial support and to Director IICT for constant encouragement.

References and notes

1. (a) Rao, Y. S. *Chem. Rev.* **1976**, *76*, 625–627; (b) Fukusaki, E.; Senda, S.; Nakazono, Y.; Omata, T. *Tetrahedron* **1991**, *47*, 6223–6230; (c) Mori, K. *Tetrahedron* **1989**, *45*, 3233–3298; (d) Wheeler, J. W.; Happ, G. M.; Araujo, J.; Pasteels, J. M. *Tetrahedron Lett.* **1972**, *13*, 4635–4638; (e) Bloch, R.; Gilbert, L. *J. Org. Chem.* **1987**, *52*, 4603–4605.
2. (a) Gunasekera, S. P.; Mc Carthy, P. J.; Kelly-Borges, M.; Lobkovsky, E.; Clardy, J. *J. Am. Chem. Soc.* **1996**, *118*, 8759–8760; (b) Avcibasi, H.; Anil, H. *Phytochemistry* **1987**, *26*, 2852–2854; (c) Miles, D. H.; Chittawong, V.; Lho, D.-S.; Payne, A.-M.; de La Cruz, A. A.; Gomez, E. D.; Weeks, J. A.; Atwood, J. L. *J. Nat. Prod.* **1991**, *54*, 286–289; (d) Hoffmann, H. M. R.; Rabe, J. *Angew. Chem. Int. Ed. Engl.* **1985**, *24*, 94–110; (e) Boukoulas, J.; McCann, L. C. *Tetrahedron Lett.* **2011**, *52*, 1202–1204.
3. (a) Hentzer, M.; Eberl, L.; Nielsen, J.; Giviskov, M. *Biodrugs* **2003**, *17*, 241–250; (b) Hjelmgaard, T.; Persson, T.; Rasmussen, T. B.; Givskov, M.; Nielsen, J. *Bioorg. Med. Chem.* **2003**, *11*, 3261–3271; (c) Fusetani, N. *Nat. Prod. Rep.* **2004**, *21*, 94–104.
4. (a) Cateni, F.; Zillic, J.; Zacchigna, M.; Bonivento, P.; Frausin, F.; Carcia, V. *Eur. J. Med. Chem.* **2006**, *41*, 192–200; (b) Marcos, I. S.; Escola, M. A.; Moro, R. F.; Basabe, P.; Diez, D.; Sanz, F.; Mollinedo, F.; dela Iglesia-Vicente, J.; Sierrac, B. G.; Urones, J. G. *Bioorg. Med. Chem.* **2007**, *15*, 5719–5737; (c) Takahashi, M.; Dodo, K.; Sugimoto, Y.; Aoyagi, Y.; Yamada, Y.; Hashimoto, Y.; Shirai, R. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 2571–2574; (d) Brohm, D.; Philippe, N.; Metzger, S.; Bhargava, A.; Muller, O.; Lieb, F.; Waldmann, H. *J. Am. Chem. Soc.* **2002**, *124*, 13171–13178.
5. Li, D. H.; Zhu, T. J.; Liu, H. B.; Fang, C. Y.; Gu, Q. Q.; Zhu, W. M. *Arch. Pharm. Res.* **2006**, *29*, 624–626.
6. Ma, S.; Shi, Z.; Yu, Z. *Tetrahedron* **1999**, *55*, 12137–12148.
7. Fragoso-Serrano, M.; Gibbons, S.; Perda-Miranda, R. *Planta Med.* **2005**, *71*, 278–280.
8. Mattinez, M. *Las Plantas Medicinales de Mexico*; Editorial Botas: Mexico, 1989. p. 508.
9. Malan, K.; Pelissier, Y.; Marion, C.; Blaise, A.; Blessiere, J. *Planta Med.* **1988**, *54*, 531–532.
10. Perda-Miranda, R.; Hernandez, L.; Villavicencio, M. J.; Novelo, M.; Ibarra, P. *J. Nat. Prod.* **1993**, *56*, 583–593.
11. (a) Chanti Babu, D.; Selavam, J. J. P.; Reddy, D. K.; Shekhar, V.; Venkateswarlu, Y. *Tetrahedron* **2011**, *67*, 3815–3819; (b) Reddy, D. K.; Shekhar, V.; Prabhakar, P.; Chanti Babu, D.; Ramesh, D.; Siddhardha, B.; Murthy, U. S. N.; Venkateswarlu, Y. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 997–1000; (c) Ramesh, D.; Rajaram, S.; Prabhakar, P.; Ramulu, U.; Reddy, D. K. *Helv. Chim. Acta* **2011**, *94*, 1226–1233; (d) Shekhar, V.; Reddy, D. K.; Suresh, V.; Chanti Babu, D.; Venkateswarlu, Y. *Tetrahedron Lett.* **2010**, *51*, 946–948; (e) Rajesh, K.; Suresh, V.; Selvam, J. J. P.; Rao, C. B.; Venkateswarlu, Y. *Synthesis* **2010**, *8*, 1381–1385; (f) Prabhakar, P.; Rajaram, S.; Reddy, D. K.; Shekhar, V.; Venkateswarlu, Y. *Tetrahedron: Asymmetry* **2010**, *21*, 216–221.
12. (a) Colobert, F.; Genet, J.-P. *Tetrahedron Lett.* **1985**, *26*, 2779–2782; (b) Babudri, F.; Fiandanese, V.; Hasan, O.; Punzi, A.; Naso, F. *Tetrahedron* **1998**, *54*, 4327–4336.
13. (a) Reddy, M. V. R.; Rearick, J. P.; Hoch, N.; Ramachandran, P. V. *Org. Lett.* **2001**, *3*, 19–20; (b) Midland, M. M.; McDowell, D. C.; Hatch, R. L.; Tramontano, A. *J. Am. Chem. Soc.* **1980**, *102*, 867–869; (c) Stille, J. K.; Sweet, M. P. *Tetrahedron Lett.* **1989**, *30*, 3645–3648.
14. Rossi, R.; Bellina, F.; Catanese, A.; Manninab, L.; Valensinc, D. *Tetrahedron* **2000**, *56*, 479–487.
15. (a) Vaz, B.; Pereira, R.; Perez, M.; Alvarez, R.; de Lera, A. R. *J. Org. Chem.* **2008**, *73*, 6534–6541; (b) Andreini, B. P.; Carpita, A.; Rossi, R.; Scamuzzi, B. *Tetrahedron* **1989**, *45*, 5621–5640; (c) Hulot, C.; Amiri, S.; Blond, G.; Schreiner, P. R.; Suffert, J. *J. Am. Chem. Soc.* **2009**, *131*, 13387–13398.
16. (a) Caddick, S.; Shanmugathasan, S.; Brasseur, D.; Delisser, V. M. *Tetrahedron Lett.* **1997**, *38*, 5735–5736; (b) Somfai, P.; Marchand, P.; Torsell, S.; Lindstrom, U. M. *Tetrahedron* **2003**, *59*, 1293–1299.
17. (a) Still, W. C.; Gennari, C. *Tetrahedron Lett.* **1983**, *24*, 4405–4408; (b) Horita, K.; Sakurai, Y.; Nagasawa, M.; Yonemitsu, O. *Chem. Pharm. Bull.* **1997**, *45*, 1558–1572; (c) Krishna, P. R.; Reddy, P. S. *Tetrahedron* **2007**, *63*, 3995–3999.
18. Spectral data for selected compounds:
Compound **6**: $[\alpha]_D^{25}$ −40.4 (*c* 2.1, $CHCl_3$); IR (neat): 3413, 2932, 2860, 1613, 1249, 1083, 838, 777 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.21 (d, 2H, *J* = 8.3 Hz), 6.84 (d, 2H, *J* = 8.3 Hz), 4.47 (s, 2H), 4.39–4.30 (m, 2H), 3.79 (s, 3H), 3.78–3.72 (m, 1H) 3.67–3.50 (m, 2H), 2.62 (br s, 2H), 1.69–1.56 (m, 2H), 1.44–1.26 (m, 4H), 0.91 (t, 3H, *J* = 6.8 Hz), 0.89 (s, 9H), 0.09 (d, 6H, *J* = 6.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.2, 129.6, 129.3, 113.7, 88.0, 81.4, 73.3, 73.1, 70.2, 63.5, 62.7, 55.1, 38.1, 27.2, 25.6, 22.2, 18.1, 13.9, -4.6, -5.1; HRMS (ESI): calcd for $C_{24}H_{40}O_5NaSi$ $[M+Na]^+$ 459.2537; found 459.2523; *Compound* **5**: $[\alpha]_D^{25}$ −44.3 (*c* 1.2, $CHCl_3$); IR (neat): 2956, 2867, 1731, 1374, 1230, 1054 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 6.18–6.08 (m, 1H), 5.95 (d, 1H, *J* = 11.3 Hz), 5.65 (t, 1H, *J* = 6.8 Hz), 5.39 (t, 1H, *J* = 6.8 Hz), 4.42 (d, 1H, *J* = 6.0 Hz), 3.76 (s, 3H), 2.07 (s, 3H), 1.81–1.71 (m, 2H), 1.55–1.24 (m, 10H), 0.91 (t, 3H, *J* = 6.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.8, 165.4, 144.3, 123.3, 111.4, 84.1, 81.6, 77.1, 70.8, 63.8, 51.5, 34.2, 27.2, 26.9, 26.4, 22.1, 20.9, 13.8; HRMS (ESI): calcd. for $C_{18}H_{26}O_6Na$ $[M + Na]^+$ 361.1621; found 361.1617; Compound **1:** $[\alpha]_D^{25}$ −43.7 (*c* 0.18, $CHCl_3$); IR (neat): 3444, 2924, 2855, 1752, 1243, 1044 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.55 (dd, 1H, *J* = 6.1, 1.8 Hz), 6.22 (dd, 1H, *J* = 6.1, 1.8 Hz), 5.56–5.33 (m, 3H), 5.16 (dt, 1H, *J* = 6.1, 1.8 Hz), 4.96 (dd, 1H, *J* = 7.8, 6.1 Hz), 3.70 (d, 1H, *J* = 3.8 Hz), 2.05 (s, 3H), 1.79-1.48 (m, 2H), 1.44–1.18 (m, 4H), 0.92 (t, 3H, *J* = 7.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.5, 171.8, 153.3, 133.1, 129.3, 123.2, 84.1, 71.0, 67.1, 33.6, 27.1, 22.4, 21.3, 13.9; HRMS (ESI): calcd for $C_{14}H_{20}O_5Na$ $[M+Na]^+$ 291.1202; found 291.1200.