Tetrahedron Letters 51 (2010) 5736–5739

Contents lists available at ScienceDirect

Tetrahedron Letters

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

Stereoselective total synthesis of (+)-anamarine via cross-metathesis protocol

Gowravaram Sabitha *, C. Nagendra Reddy, Peddabuddi Gopal, J. S. Yadav

Organic Division I, Indian Institute of Chemical Technology, Hyderabad 500 007, India

ARTICLE INFO

Article history:
Received 28 July 2010
Revised 23 August 2010
Accepted 25 August 2010
Available online 31 August 2010

Keywords:
δ-Lactone
Sharpless epoxidation
Sharpless dihydroxylation
Red-Al
Cross-metathesis

ABSTRACT

A convergent stereoselective total synthesis of (+)-anamarine via cross-metathesis (CM) protocol starting from 2-butyn-1,4-diol and vinyl lactone is reported. Other key features of the strategy include the use of Sharpless asymmetric epoxidation, Sharpless dihydroxylation, and Red-Al reduction.

Anamarine (**1**)[1] is a member of the polyoxygenated 5,6-dihydro-2*H*-pyran-2-one (α,β-unsaturated δ-lactone)-containing natural product family isolated from the flowers and leaves of a Peruvian *Hyptis*. Other members of the α,β-unsaturated δ-lactone family are spicigerolide (**2**),[2] hyptolide (**3**),[3] synrotolide diacetate (**4**),[4] and synargentolide (**5**)[5] (Fig. 1) isolated from the *Hyptis* and *Syncolostemon* and related genera of the family Lamiaceae. These compounds have been found to exhibit antibacterial, antifungal, as well as cytotoxicity against human tumor cells.[6] In addition, 6-substituted-α,β-unsaturated-δ-lactones have been reported to inhibit HIV protease,[7] induce apoptosis,[8,9] and have proven to be anti-leukemic,[10] along with having many other relevant pharmacological properties.[11] Thus, these lactones have attracted the attention of synthetic chemists. Recently we have reported the first synthesis of synargentolide.[12] In continuation of our efforts toward the synthesis of naturally occurring six-membered lactones,[13] we became interested in the synthesis of the natural lactone anamarine by a convergent strategy using a cross-metathesis (CM) protocol. So far three syntheses[14] have been reported for **1**. Herein, we report the stereoselective total synthesis of (+)-anamarine **1** from the readily available starting materials 2-butyn-1,4-diol and 3-butyn-1-ol.

Retrosynthetic analysis reveals that the target compound **1** (Scheme 1) can be obtained by CM reaction of olefin **6** and vinyl lactone **7**. The substrate **6** in turn could be made from the commercially available 2-butyn-1,4-diol by sequential reactions, whereas, the vinyl lactone **7**[13o] is accessible from 3-butyn-1-ol.

Accordingly, the synthesis of **1** starts with the readily available 2-butyn-1,4-diol **8** (Scheme 2) that was subjected to selective monobenzylation to afford the propargyl alcohol **9**. Partial reduction of the triple bond using LAH gave low yields of product along with an unknown by-product. However, using Red-Al in THF, the problem was solved and the required allylic alcohol **10** was obtained in a very good yield (90%). The alcohol **10** was subjected to Sharpless asymmetric epoxidation [(+)-DIPT/Ti(O*i*Pr)$_4$/TBHP/−20 °C, 24 h, 92%] to afford epoxy alcohol **11**, which was converted into propargylic alcohol **13** by a two-step process; first by converting to chloro epoxy compound **12** which on elimination using

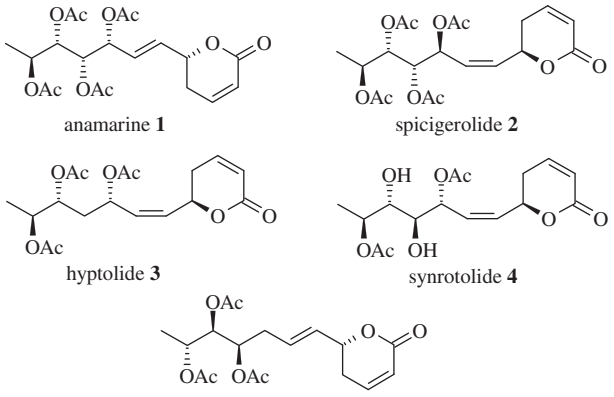
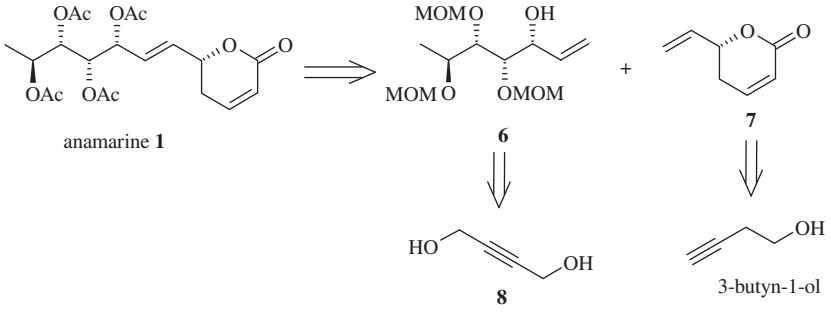


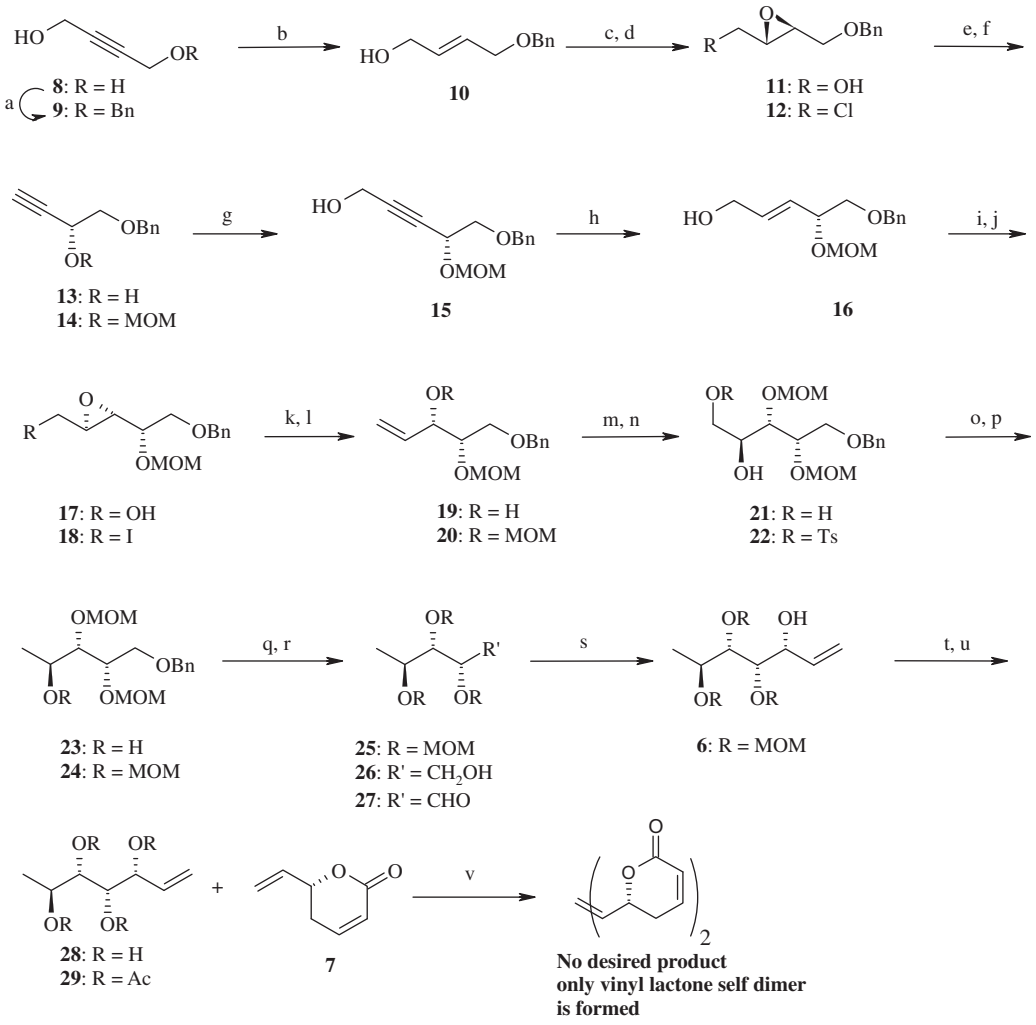
Figure 1. Polyoxygenated 5,6-dihydro-2*H*-pyran-2-one (α,β-unsaturated δ-lactone)-containing natural products.

* Corresponding author. Tel.: +91 40 27191629; fax: +91 40 27160512.
E-mail address: gowravaramsr@yahoo.com (G. Sabitha).

0040-4039/$ - see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2010.08.077

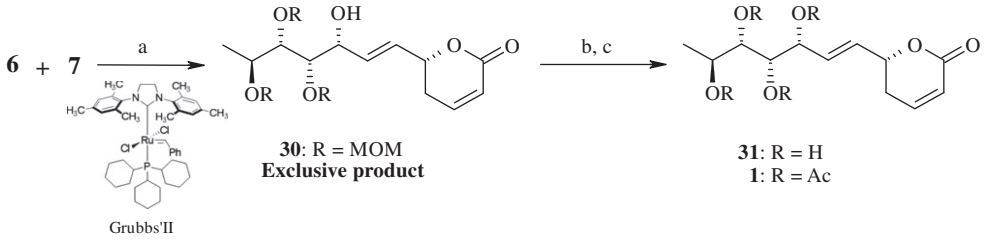


Scheme 1. Retrosynthesis.



Scheme 2. Reagents and conditions: (a) NaH, BnBr, anhydrous THF, 0 °C–rt, 24 h, 53%; (b) Red-Al, anhydrous THF, rt, 1 h, 90%; (c) $Ti(O^iPr)_4$, (+)-DIPT, TBHP, anhydrous CH_2Cl_2, −20 °C, 24 h, 92%; (d) PPh_3, $NaHCO_3$, anhydrous CCl_4, reflux, 3 h, 84%; (e) ^{n}BuLi, anhydrous THF, −78 °C, 3 h, 81%; (f) MOMCl, DIPEA, anhydrous CH_2Cl_2, 0 °C–rt, 2 h, 91%; (g) EtMgBr, $(CH_2O)_n$, anhydrous THF, rt, 5 h, 75%; (h) Red-Al, anhydrous THF, rt, 1 h, 94%; (i) $Ti(O^iPr)_4$, (−)-DIPT, TBHP, anhydrous CH_2Cl_2, −20 °C, 24 h, 94%; dr (49:1) (j) PPh_3, imidazole, I_2, Et_2O/AcN, (3:1) 0 °C–rt, 0.5 h, 92%; (k) Zn dust, EtOH, reflux, 1 h, 90%; (l) MOMCl, DIPEA, anhydrous CH_2Cl_2, 0 °C–rt, 2 h, 92%; (m) AD-mix-β, ^{t}BuOH/H_2O (1:1), 0 °C, 6 days, 90%; dr (9:1); (n) TsCl, TEA, $^n Bu_2SnO$, anhydrous CH_2Cl_2, 0 °C–rt, 1 h, 91%; (o) LAH, anhydrous THF, reflux, 1 h, 82%; (p) MOMCl, DIPEA, anhydrous CH_2Cl_2, 0 °C–rt, 2 h, 93%; (q) Pd/C, H_2, EtOAc, rt, 16 h, 95%; (r) $(COCl)_2$, DMSO, TEA, anhydrous CH_2Cl_2, −78 °C, 2 h, 92%; (s) vinylmagnesium bromide, $MgBr_2$–Et_2O, anhydrous CH_2Cl_2, −78 °C, 1 h, 74%; de (>95%); (t) 3 N HCl MeOH/AcN (1:1), 0 °C–rt, 8 h, 80%; (u) Ac_2O, TEA, DMAP, CH_2Cl_2, 0 °C–rt,0.5 h, 91%; (v) Grubb's-II, dry CH_2Cl_2, reflux, 5 h (90%).

n-BuLi afforded the propargylic alcohol **13** (83% yield over two steps). The hydroxyl group in **13** was protected as its MOM ether (MOMCl/DIPEA/CH_2Cl_2/0 °C to rt, 2 h, 91%) to afford **14**. The MOM ether **14** was treated with Grignard reagent prepared from ethyl bromide and magnesium followed by quenching with *para* formaldehyde in dry THF to afford **15** in 75% yield. In order to get the *trans*-allyl alcohol, compound **15** was treated with Red-Al in THF at rt, which reduced the alkyne to the desired *trans*-olefin **16** in 94% yield. In the next step, olefin **16** was subjected to Sharpless asymmetric epoxidation using (−)-DIPT, Ti(O*i*Pr)$_4$, and TBHP to furnish the desired epoxy alcohol **17**, which was converted into the corresponding epoxy iodide **18** in 92% yield. Compound **18** on



Scheme 3. Reagents and conditions: (a) anhydrous CH_2Cl_2, reflux, 0.5 h, 86%; (b) 3 N HCl, MeOH/AcCN (1:1), 0 °C–rt, 8 h, 80%; (c) Ac_2O, TEA, DMAP, anhydrous CH_2Cl_2, 0 °C–rt, 0.5 h, 91%.

refluxing in ethanol in the presence of Zn dust eliminated to afford allylic alcohol **19** and the resulting alcohol was protected as MOM ether **20**. Asymmetric dihydroxylation[15] of **20** using AD-mix-β in $^tBuOH/H_2O$ (1:1) at 0 °C gave the diol **21** in 90% yield (dr 9:1). Selective conversion of the primary hydroxyl group of **21** into a tosylate was carried out using tosyl chloride in the presence of TEA and $^nBu_2SnO$ in CH_2Cl_2 to give **22** in 91% yield, which was reduced to the methyl compound by using $LiAlH_4$ in THF in 82% yield. The secondary alcohol was protected as its MOM ether **25** and the benzyl group was removed using Pd/C, H_2 in EtOAc to afford the primary alcohol **26**, which was converted into the corresponding aldehyde **27** under Swern oxidation conditions. To create a fourth stereogenic center with the required stereochemistry, a chelation-controlled vinyl Grignard reaction[16] was performed. Thus, adding a solution of vinylmagnesium bromide in THF to the complex formed between **27** and 1 equiv of magnesium bromide etherate in CH_2Cl_2, provided the chelation-controlled product **6** in excellent yield and with high (>95%) diastereofacial selectivity.

The three MOM groups were removed and subsequently protected as acetates to give tetraacetate derivative **29**, which was expected to give directly the target molecule **1** when subjected to cross-metathesis reaction with vinyl lactone **7** using Grubb's II generation catalyst. But, this reaction failed to give the desired target **1**, instead it gave exclusively the dimer of vinyl lactone (Scheme 2).

However, the tri MOM derivative **6** underwent CM reaction smoothly with vinyl lactone **7** using Grubb's II generation catalyst to yield the desired lactone **30** (86%) exclusively (Scheme 3).

Subsequent removal of MOM groups in **30** using 3 N HCl in $MeOH/CH_3CN$ (1:1), at 0 °C afforded tetrahydroxy derivative **31** (80%). Acetylation of **31** with acetic anhydride in the presence of TEA and DMAP furnished the target lactone, anamarine **1**[17] in 91% yield. The spectral data of the synthetic compound matched with the literature values.[14c]

In summary, we accomplished the stereoselective total synthesis of (+)-anamarine via the CM protocol.

Acknowledgments

C.N.R. thanks UGC, and P.G. thanks CSIR, New Delhi for the award of fellowships.

References and notes

1. Alemany, A.; Márquez, C.; Pascual, C.; Valverde, S.; Martínez-Ripoll, M.; Fayos, J.; Perales, A. *Tetrahedron Lett.* **1979**, *20*, 3583–3586.
2. Pereda-Miranda, R.; Fragoso-Serrano, M.; Cerda-García-Rojas, C. M. *Tetrahedron* **2001**, *57*, 47–53.
3. Achmad, S. A.; Høyer, T.; Kjær, A.; Makmur, L.; Norrestam, R. *Acta Chem. Scand.* **1987**, *41B*, 599–609.
4. Coleman, M. T. D.; English, R. B.; Rivett, D. E. A. *Phytochemistry* **1987**, *26*, 1497–1499.
5. Collett, L. A.; Davies-Coleman, M. T.; Rivett, D. E. A. *Phytochemistry* **1998**, *48*, 651–656.
6. (a) Pereda-Miranda, R.; Fragoso-Serrano, M.; Cerda-Garcia-Rojas, C. M. *Tetrahedron* **2001**, *57*, 47–53; (b) Pereda-Miranda, R.; Hernandez, L.; Villavicencio, M. J.; Novelo, M.; Ibarra, P.; Chai, H.; Pezzuto, J. M. *J. Nat. Prod.* **1993**, *56*, 583–593.
7. (a) Romines, K. R.; Chrusciel, R. A. *Curr. Med. Chem.* **1995**, *2*, 825–838; (b) Aristoff, P. A. *Drugs Future* **1998**, *23*, 995–999; (c) Hagen, S. E.; Vara-Prasad, J. V. N.; Tait, B. D. *Adv. Med. Chem.* **2000**, *5*, 159–195; (d) Hagen, S. E.; Domagala, J. M.; Gajda, C.; Lovdahl, M.; Tait, B. D.; Wise, E.; Holler, T.; Hupe, D.; Nouhan, C.; Urumov, A.; Zeikus, G.; Zeikus, E.; Lunney, E. A.; Pavlovsky, A.; Gracheck, S. J.; Saunders, J. M.; VanderRoest, S.; Brodfuehrer, J. *J. Med. Chem.* **2001**, *44*, 2319–2332; (e) Agrawal, V. K.; Singh, J.; Mishra, K. C.; Khadikar, P. V.; Jaliwala, Y. A. *ARKIVOC* **2006**, 162–177.
8. (a) Inayat-Hussain, S. H.; Annuar, B. O.; Din, L. B.; Taniguchi, N. *Toxicol. Lett.* **2002**, *131*, 153–159; (b) Inayat-Hussain, S. H.; Annuar, B. O.; Din, L. B.; Ali, A. M.; Ross, D. *Toxicol. In Vitro* **2003**, *17*, 433–439; (c) Chan, K. M.; Rajab, N. F.; Ishak, M. H. A.; Ali, A. M.; Yusoff, K.; Din, L. B.; Inayat-Hussain, S. H. *Chem. Biol. Interact.* **2006**, *159*, 129–140.
9. For further literature related to this important biological property, see, for example: (a) Blatt, N. B.; Glick, G. D. *Bioorg. Med. Chem.* **2001**, *9*, 1371–1384; (b) Huang, Z. W. *Chem. Biol.* **2002**, *9*, 1059–1072.
10. Kikuchi, H.; Sasaki, K.; Sekiya, J.; Maeda, Y.; Amagai, A.; Kubohara, Y.; Ohsima, Y. *Bioorg. Med. Chem.* **2004**, *12*, 3203–3214.
11. See, for example: (a) Stampwala, S. S.; Bunge, R. H.; Hurley, T. R.; Willmer, N. E.; Brankiewicz, A. J.; Steinman, C. E.; Smitka, T. A.; French, J. C. *J. Antibiot.* **1983**, *36*, 1601–1605; (b) Nagashima, H.; Nakamura, K.; Goto, T. *Biochem. Biophys. Res. Commun.* **2001**, *287*, 829–832; (c) Raoelison, G. E.; Terreaux, C.; Queiroz, E. F.; Zsila, F.; Simonyi, M.; Antus, S.; Randriantsoa, A.; Hostettmann, K. *Helv. Chim. Acta* **2001**, *84*, 3470–3476; (d) Lewy, D. S.; Gauss, C.-M.; Soenen, D. R.; Boger, D. L. *Curr. Med. Chem.* **2002**, *9*, 2005–2032; (e) Larsen, A. K.; Escargueil, A. E.; Skladanowski, A. *Pharmacol. Ther.* **2003**, *99*, 167–181; (f) Richetti, A.; Cavallaro, A.; Ainis, T.; Fimiani, V. *Immunopharmacol. Immunotoxicol.* **2003**, *25*, 441–449; (g) Koizumi, F.; Ishiguro, H.; Ando, K.; Kondo, H.; Yoshida, M.; Matsuda, Y.; Nakanishi, S. *J. Antibiot.* **2003**, *56*, 603–609.
12. Sabitha, G.; Gopal, P.; Reddy, C. N.; Yadav, J. S. *Tetrahedron Lett.* **2009**, *46*, 6298–6302.
13. (a) Sabitha, G.; Sudhakar, K.; Reddy, N. M.; Rajkumar, M.; Yadav, J. S. *Tetrahedron Lett.* **2005**, *46*, 6567–6570; (b) Sabitha, G.; Narjis, F.; Swapna, R.; Yadav, J. S. *Synthesis* **2006**, *17*, 2879–2884; (c) Sabitha, G.; Reddy, E. V.; Yadagiri, K.; Yadav, J. S. *Synthesis* **2006**, *19*, 3270–3274; (d) Sabitha, G.; Sudhakar, K.; Yadav, J. S. *Tetrahedron Lett.* **2006**, *47*, 8599–8602; (e) Sabitha, G.; Bhaskar, V.; Yadav, J. S. *Tetrahedron Lett.* **2006**, *47*, 8179–8181; (f) Sabitha, G.; Swapna, R.; Reddy, E. V.; Yadav, J. S. *Synthesis* **2006**, *24*, 4242–4246; (g) Sabitha, G.; Bhikshapathi, M.; Yadav, J. S. *Synth. Commun.* **2007**, *37*(4), 561–569; (h) Sabitha, G.; Gopal, P.; Yadav, J. S. *Synth. Commun.* **2007**, *37*, 1495–1502; (i) Sabitha, G.; Yadagiri, K.; Yadav, J. S. *Tetrahedron Lett.* **2007**, *48*, 1651–1652; (j) Sabitha, G.; Yadagiri, K.; Yadav, J. S. *Tetrahedron Lett.* **2007**, *48*, 8065–8068; (k) Sabitha, G.; Bhaskar, V.; Yadav, J. S. *Synth. Commun.* **2008**, *38*, 1–12; (l) Sabitha, G.; Bhaskar, V.; Siva Sankara Reddy, S.; Yadav, J. S. *Tetrahedron* **2008**, *64*(44), 10207–10213; (m) Sabitha, G.; Bhaskar, V.; Siva Sankara Reddy, S.; Yadav, J. S. *Synthesis* **2009**, 3285; (n) Sabitha, G.; Gopal, P.; Reddy, C. N.; Yadav, J. S. *Synthesis* **2009**, 3301; (o) Sabitha, G.; Fatima, N.; Gopal, P.; Reddy, C. N.; Yadav, J. S. *Tetrahedron: Asymmetry* **2009**, *20*, 184–191; (p) Sabitha, G.; Fatima, N.; Reddy, E. V.; Yadav, J. S. *Tetrahedron Lett.* **2008**, *49*(42), 6087–6089; (q) Synthesis of Obolactone, Sabitha, G.; Prasad, M. N.; Shankaraiah, K. S.; Jadav, J. S. *Synthesis* **2010**, 1171–1175; (r) Sabitha, G.; Reddy, N. M.; Prasad, M. N.; Yadav, J. S. *Helv. Chim. Acta* **2009**, *92*, 967; (s) Sabitha, G.; Bhaskar, V.; Siva Sankara Reddy, S.; Yadav, J. S. *Helv. Chim. Acta* **2010**, *93*, 329–338.
14. (a) Lorenz, K.; Frieder, L. W. *Tetrahedron Lett.* **1987**, *28*, 6437–6440; (b) Diaz-Oltra, S.; Murga, J.; Falomir, E.; Carda, M.; Marco, A. J. *Tetrahedron* **2004**, *60*, 2979–2985; (c) Gao, D.; O' Doherty, G. A. *J. Org. Chem.* **2004**, *70*, 9932–9939.
15. (a) Crispino, G. A.; Jeong, K. S.; Kolb, H. C.; Wang, Z. M.; Xu, D.; Sharpless, K. B. *J. Org. Chem.* **1993**, *58*, 3785; (b) Ko, S. Y.; Malik, M. *Tetrahedron Lett.* **1993**, *34*, 4675; (c) Takano, S.; Yoshimitsu, T.; Ogasawara, K. *J. Org. Chem.* **1994**, *59*, 54; (d) Vidari, G.; Giori, A.; Dapiaggi, A.; Lanfranchi, G. *Tetrahedron Lett.* **1993**, *34*, 6925.
16. (a) Venkatesan, K.; Srinivasan, K. V. *Tetrahedron: Asymmetry* **2008**, *19*, 209–215; (b) Keck, G. E.; Andrus, M. B.; Romer, D. R. *J. Org. Chem.* **1991**, *56*, 417–420.
17. Analytical data of all the new compounds are given below. *(R)-5-(Benzyloxy)-4-(methoxymethoxy)pent-2-yn-1-ol* (**15**): $[\alpha]_D^{25} = -79.6$ (*c* 1, $CHCl_3$); IR (KBr) 3426, 3030, 2929, 1452, 1027 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.34–7.27 (m, 5H, ArH), 4.88 (d, *J* = 6.0 Hz, 1H,), 4.61 (d, *J* = 6.7 Hz, 1H), 4.59 (m, 1H), 4.53 (ABq,

J = 12.5, 18.2 Hz, 2H, C**H**$_2$–OAr), 4.22 (d, J = 1.5 Hz, 2H), 3.62 (d, J = 5.2 Hz, 2H), 3.37 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 137.6, 128.3, 127.5, 127.4, 94.1, 85.0, 81.1, 73.3, 72.1, 65.1, 55.5, 50.5; HRMS calcd for $C_{14}H_{18}O_4Na$: 273.1102; found: 273.1112.

((2R,3S)-3-((S)-2-(Benzyloxy)-1-(methoxymethoxy)ethyl)oxiran-2-yl)methanol (**17**): $[\alpha]_D^{25} = +1.0$ (c 1, $CHCl_3$); IR (KBr) 3444, 2897, 1453, 1101, 1031 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.36–7.20 (m, 5H, ArH), 4.77 (d, J = 6.6 Hz, 1H, CH), 4.67 (d, J = 6.4 Hz, 1H, CH), 4.53 (ABq, J = 12.0, 14.0 Hz, 2H, C**H**$_2$–OAr), 3.84 (d, J = 12.4 Hz, 1H), 3.65–3.51 (m, 4H), 3.36 (s, 3H, CH_3); 3.10 (d, J = 2.2 Hz, 1H) 3.02 (d, J = 1.32 Hz, 1H), 1.70 (brds, 1H, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 137.7, 128.3, 127.6, 127.4, 95.7, 75.6, 73.3, 70.0, 61.1, 56.1, 55.5, 55.4; HRMS calcd for $C_{14}H_{20}O_5Na$: 291.1208; found: 291.1214.

1-(((2S,3S)-2,3-Bis(methoxymethoxy)pent-4-enyloxy)methyl)benzene (**20**): $[\alpha]_D^{25} = +18.8$ (c 1, $CHCl_3$); IR (KBr) 2891, 1452, 1151,1033, 919 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.34–7.25 (m, 5H, ArH), 5.78 (m, 1H), 5.31 (dd, J = 2.2,17.3 Hz, 1H), 5.24 (dd, J = 3.0, 10.5 Hz,1H), 4.83–4.61 (m, 4H), 4.54 (ABq, J = 12.0, 15.1 Hz, 2H, C**H**$_2$–OAr); 4.23 (m, 1H), 3.78 (m, 1H), 3.67–3.48 (m, 2H), 3.36 (s, 3H, CH_3), 3.33 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 137.6,134.2, 127.8 127.1, 127.0, 118.1, 96.5, 93.7, 77.7, 76.3,72.9, 69.6, 55.2, 55.1; HRMS calcd for $C_{16}H_{24}O_5Na$: 319.1521; found: 319.1517.

(2S,3S,4S)-5-(Benzyloxy)-3,4-bis(methoxymethoxy)pentane-1,2-diol (**21**): $[\alpha]_D^{25} = -11.0$ (c 1, $CHCl_3$); IR (KBr) 3380, 2933, 1452, 1153, 1026 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.37–7.21 (m, 5H, ArH), 4.79–4.60 (m, 4H), 4.53 (q, J = 12.2, 13.4 Hz, 2H, C**H**$_2$–OAr), 4.03 (t, J = 5.4 Hz, 1H), 3.79–3.58 (m, 6H), 3.39 (s, 3H, CH_3); 3.38 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 137.6, 128.3, 127.7, 127.6, 98.4, 97.4, 78.6, 76.4, 73.4, 70.7, 69.4, 63.1, 56.3, 55.9; HRMS calcd for $C_{16}H_{26}O_7Na$:353.1576; found: 353.1564.

1-(((2S,3S,4S)-2,3,4-Tris(methoxymethoxy)pentyloxy)methyl)benzene (**24**): $[\alpha]_D^{25} = +1.5$ (c 1, $CHCl_3$); IR (KBr) 2934, 2891, 1452,1150, 917 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.32–7.27 (m, 5H, ArH), 4.74–4.57 (m, 6H), 4.52 (q, J = 12.0, 14.3 Hz, 2H, C**H**$_2$–OAr), 3.90–3.74 (m, 3H), 3.63–3.51 (m, 2H, CH_2), 3.37 (s, 3H, CH_3), 3.35 (s, 3H, CH_3), 3.33 (s, 3H, CH_3), 1.21 (d, J = 6.7 Hz, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.0, 128.3, 127.7, 127.6, 97.7, 97.2, 95.1, 79.6, 76.5, 73.3, 73.2, 70.2, 56.0, 55.7, 55.3, 16.3; HRMS calcd for $C_{18}H_{30}O_7Na$: 381.1889; found: 381.1900.

(3R,4S,5S,6S)-4,5,6-Tris(methoxymethoxy)hept-1-en-3-ol (**6**): $[\alpha]_D^{25} = -16.1$ (c 1, $CHCl_3$); IR (KBr) 3451, 2932, 1150, 1029, 918 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.97 (m,1H), 5.40 (td, J = 1.5,10.5 Hz,1H), 5.21 (td, J = 1.5, 11 Hz,1H), 4.81–4.64 (m, 6H), 4.34–4.25 (m, 1H), 3.90 (m,1H), 3.74 (m, 1H), 3.63 (ABq, J = 4.7, 9.6 Hz,1H), 3.44 (s, 3H, CH_3), 3.43 (s, 3H, CH_3), 3.38 (s, 3H, CH_3), 1.27 (d, J = 6.6 Hz, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 137.4, 116.8, 98.5, 97.6, 95.2, 82.5, 79.8, 72.7, 71.8, 56.1, 56.0, 55.4, 16.4; HRMS calcd for $C_{13}H_{26}O_7Na$: 317.1576; found: 317.1578.

*(R)-5,6-Dihydro-6-((E,3R,4S,5S,6S)-3-hydroxy-4,5,6-tris(methoxymethoxy)hept-1-enyl)*pyran-*2-one* (**30**): $[\alpha]_D^{25} = +5.2$ (c 1, $CHCl_3$); IR (KBr) 3444, 2930, 1722, 1246, 1029, 916 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.89 (m,1H), 6.10–5.93 (m, 3H), 4.98 (m, 1H), 4.82–4.63 (m, 6H), 4.22 (m, 1H), 3.88 (dt, J = 5.5, 24.2 Hz, 1H), 3.71 (dt, J = 3.7, 30.7 Hz, 1H), 3.64 (m, 1H), 3.43 (s, 3H, CH_3), 3.42 (s, 3H, CH_3), 3.37 (s, 3H, CH_3), 2.48 (m, 2H), 1.28 (d, J = 6.5 Hz, 3H,CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 163.8, 144.4, 132.6, 128.7, 121.6, 98.3, 97.7, 95.2, 82.3, 79.7, 76.3, 73.5, 72.7, 56.1, 55.9, 55.4, 29.4, 16.4; HRMS calcd for $C_{18}H_{30}O_9Na$: 413.1787; found: 413.1808.

Anamarine (**1**): white solid: mp = 109–111 °C; $[\alpha]_D^{25} = +17.8$ (c 0.3, $CHCl_3$); IR (KBr) 2925, 1739, 1374, 1023, 974 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.88 (ddd, J = 3.5, 5.2, 9.9 Hz, 1H), 6.05 (ddd, J = 1.7, 1.7, 9.9 Hz, 1H), 5.88–5.74 (m, 2H), 5.36 (dd, J = 5.2, 7.2 Hz, 1H), 5.30 (dd, J = 3.5, 7.2 Hz, 1H), 5.17 (dd, J = 3.5, 7.0 Hz,1H), 4.96 (m, 1H) 4.90 (dq, J = 6.4, 6.4 Hz, 1H), 2.45 (m, 2H), 2.11 (s, 3H, CH_3), 2.07 (s, 3H, CH_3), 2.06 (s, 3H, CH_3), 2.03 (s, 3H, CH_3), 1.17 (d, J = 6.4 Hz, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.0, 169.8, 169.7, 169.5, 163.4, 144.5, 133.0, 125.6, 121.5, 75.9, 71.9, 71.5, 70.4, 67.5, 29.4, 21.0, 20.9, 20.8, 20.7, 15.9; HRMS calcd for $C_{20}H_{26}O_{10}Na$: 449.1423; found: 449.1434.