Tetrahedron 65 (2009) 8132–8138

Contents lists available at ScienceDirect

Tetrahedron

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

Synthesis of macrocyclic scaffolds suitable for diversity-oriented synthesis of macrolides

Michael E. Grimwood, Henrik C. Hansen *

Department of Chemistry, University of Calgary, 2500 University Drive NW, Calgary, Alberta T2N 1N4, Canada

ARTICLE INFO

Article history:
Received 27 April 2009
Received in revised form 28 July 2009
Accepted 29 July 2009
Available online 6 August 2009

ABSTRACT

Synthesis of macrocyclic glycal-based scaffolds for diversity-oriented synthesis was studied and demonstrated using macrocyclic enyne ring-closing metathesis. The roles of ring size, alkyne substitution, and orientation relative to the glycal were studied. In all cases, the cyclization showed preference for the thermodynamically favored *endo*-mode of closure and a trans-double bond at the ring-closure site, leaving macrocyclic scaffolds all containing multiple orthogonal functional groups available for further diversification.

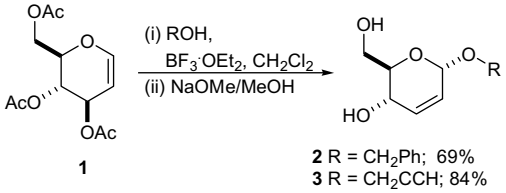
1. Introduction

Genomics and proteomics have created a tremendous need for diverse and novel organic molecules that can be used to identify and study the functions of uncharacterized proteins and their involvement in diseases.[1] diversity-oriented synthesis (DOS)[2] is a unique tool that allows for the generation of many structurally diverse and complex molecules applicable for the interrogation of biological systems. One of the key elements of successful DOS is efficient use of chemical reactions to increase diversity and complexity as the library evolves.[2a,3] To reduce the number of steps required to build up the core scaffolds, priority is given to reactions where the products, without further manipulation, may serve as starting materials for the next reactions. diversity-oriented synthesis of macrocycles[4] has not received the same amount of attention as the synthesis of smaller and traditionally more drug-like compounds. However, in nature macrocycles have many biological functions, and serve as an excellent source of molecules for the interrogation of biological systems.[5] Here, we report the investigation and development of methodology for the synthesis of macrocyclic glycal-based scaffolds suitable for DOS.[4a,b,6] We focus on macrocyclic enyne ring-closing metathesis[7] as the core reaction, and report the selective synthesis of 12- to 18-membered macrocycles, containing three or more orthogonal functional groups for further diversification.

2. Results and discussion

2.1. Synthesis of macrocyclic precursors

The desired glucal building blocks were obtained from inexpensive and commercially available tri-*O*-acetyl-D-glucal (**1**) in large gram quantities by a Ferrier reaction (Scheme 1).[8] The glycosylated alcohols were obtained in a ratio of 9:1 of α/β and the pure α diastereomer was isolated by re-crystallization. The deprotection to **2** and **3** proceeded in near quantitative yields, leaving the desired diols in excellent overall yields. The alkylation of the diol served as the first step of diversification. To facilitate selective alkylation of the 4-position, the primary alcohol was protected as a TBS ether (Scheme 2).[9] The remaining secondary alcohol was alkylated under standard conditions with alkyl bromides containing either a double or triple bond. The desired products (**5**, **6**, and **7**) were obtained in good yield following deprotection of the TBS ether. Alternatively, giving access to the 6-*O*-alkyl precursors, the primary alcohol was selectively alkylated (Scheme 2) via the corresponding tin acetal. The 6-*O*-alkylated precursors (**8**, **9**, and **10**) were isolated after chromatography.



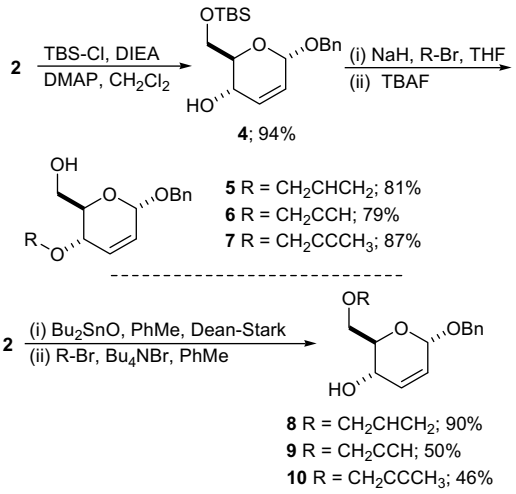
1

2 R = CH_2Ph; 69%
3 R = CH_2CCH; 84%

Scheme 1. Synthesis of glucal building blocks.

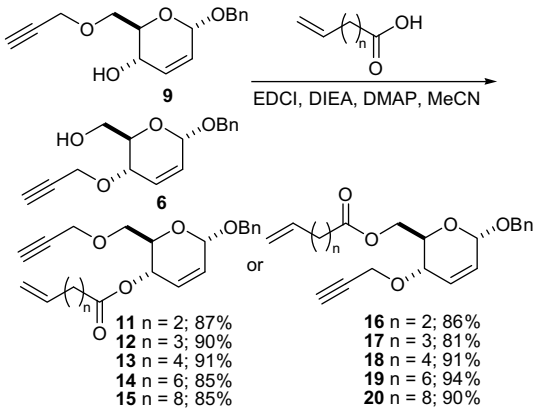
* Corresponding author at present address: Resverlogix Corp., 279 Midpark Way SE, Calgary, Alberta T2X 1M2, Canada. Tel.: +1 403 254 9252; fax: +1 403 256 8495.
E-mail address: henrik@resverlogix.com (H.C. Hansen).

0040-4020/$ – see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2009.07.088



Scheme 2. Diol alkylation. First step of diversification.

Acylation of the alcohols (**5**–**10**) served as the second step of diversification. To exemplify the methodology and to study the macrocyclization, six carboxylic acids were employed. Each carboxylic acid had different lengths and contained either a double or triple bond. The acylations proceeded in excellent yields for both the primary and secondary alcohols (Scheme 3).



Scheme 3. Acylation. Second step of diversification.

Following similar methodology four additional precursors (**21**–**24**) were synthesized (Fig. 1), allowing us to study the positioning of the alkyne as well as the significance of alkyne substitution.

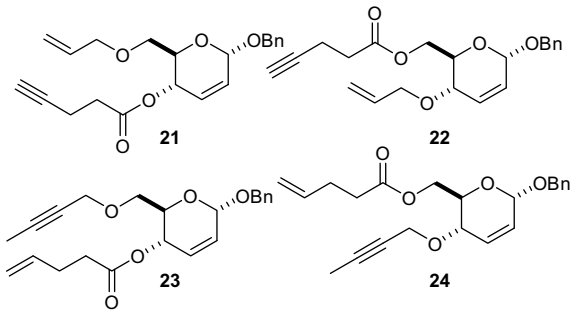
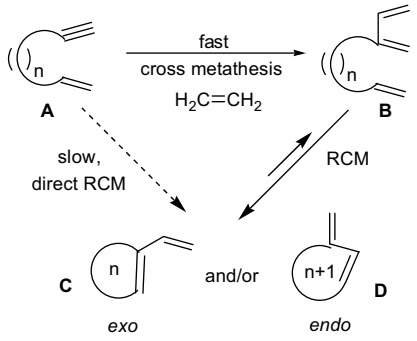


Figure 1. Additional precursors used to study macrocyclic enyne RCM.

2.2. Investigation of macrocyclization via enyne RCM

The 14 precursors (**11**–**24**) for macrocyclic enyne RCM were used to study the roles of ring size, alkyne substitution pattern, and positioning of the alkyne relative to the glycal core, as well as to identify reaction conditions suitable for the synthesis of these attractive macrocylic scaffolds for DOS. In all cases, we found that the use of Grubbs' second generation catalyst[10] was superior to the first generation catalyst. The best reaction conditions were 20 mol % catalyst and an enyne concentration of 1 mM under an ethylene atmosphere.[11]

In agreement with the proposed pathway[7a] for enyne metathesis (Scheme 4), we found that in the presence of ethylene the cyclization goes through the cross metathesis intermediate (**B**), which then undergoes RCM to the final product(s) (**C** and/or **D**).[12] In the presence of ethylene, an equilibrium between the ring closed diene (**C** and/or **D**) and the triene (**B**) should favor the formation of the thermodynamically favored product with an *E*-double bond. The *exo*/*endo* selectivity of the macrocyclic RCM was expected to be a function of ring size, where larger rings prefer the *endo*-mode of closure.



Scheme 4. RCM pathway.

2.3. Ring-closure with unsubstituted alkynes—12-membered rings

Four different cyclic enynes (**11**, **16**, **21**, **22**) were used to study macrocyclic enyne RCM on a glucal scaffold. For **11**, **16**, **21**, and **22**, differing in the position of the alkyne and alkene relative to the glucal, the reaction proceeded in good overall yield with complete consumption of starting material and without trace of the corresponding tetraenes. For compound **11**, the *endo* product was formed with high selectivity (24:1), whereas compounds **16**, **21**, and **22** exclusively gave the *endo* products (Fig. 2), demonstrating that for

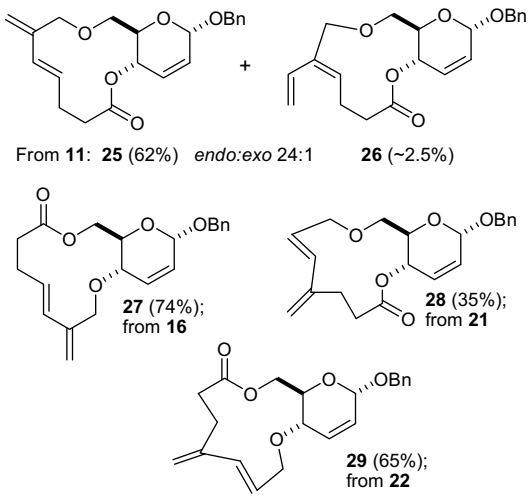


Figure 2. Macrocyclic enyne RCM to 12-membered rings with terminal alkynes.[13]

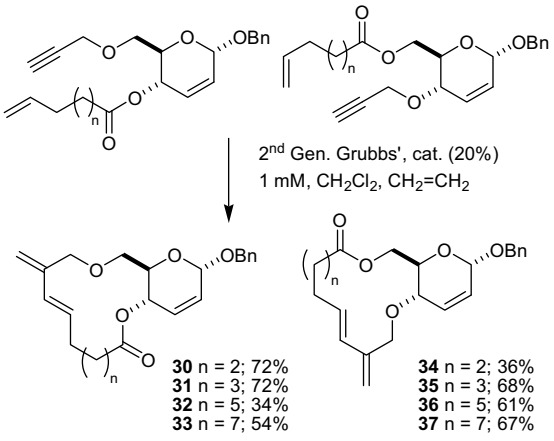
macrocyclic ring systems (≥12) the position of the reacting partners plays a minor role in the outcome of the final ring closed product (Scheme 4). For medium rings (9–11), this is likely to play a bigger role. In all cases only the trans-double bond was observed, which is in agreement with the use of ethylene atmosphere.[7a] In all cases, the desired products contain orthogonal functional groups useful for further diversification.

2.4. Ring-closure with substituted alkynes—12-membered rings

As expected, the cyclization with substituted alkynes (**23** and **24**) proved to be more complex than with the corresponding unsubstituted alkynes. Like others,[7d] we found that there was no selectivity between the *endo* and *exo* modes of closure. However, in our hands and in contrast to the literature,[7a,7d] we did not observe higher yields for substituted alkynes compared to their unsubstituted counterparts. In each case studied (**23** and **24**), we obtained a mixture of the desired product and the tetraene. Prolonging the reaction time led to extensive decomposition.

2.5. Ring-closure with unsubstituted alkynes—13- to 18-membered rings

Eight monocyclic enynes (**12**–**15** and **17**–**20**) were used to study the formation of 13- to 18-membered rings. All substrates selectively formed the *endo* product with a trans-double bond (**30–37**; Scheme 5). We believe that the *endo* selectivity is due to reduced steric hindrance during product formation. As the ring size gets larger, the sterically more demanding *endo*, but energetically favored, product becomes increasingly favored, resulting in exclusive formation of the *endo* product during the final diene RCM.



Scheme 5. Cyclization reaction to give 13- to 18-membered rings.

Typically, macrocyclization suffers from decreasing yields as the ring size increases, however, in the cases studied herein this does not seem to be the case. Thus, using this methodology for the synthesis of macrocycles for DOS is very useful.

2.6. Determination of ring size by 2D-NMR

For each cyclized product, the ring size and mode of cyclization were determined by Heteronuclear Multiple Bond Correlation (HMBC). The key correlation used to justify the *endo* products was between the *exo*-cyclic methylene protons and the allylic carbon next to the ether oxygen on the newly formed ring (**27**, Fig. 3). This correlation would be absent in rings formed via the *exo* mode of closure (**27**-*exo*, Fig. 3).

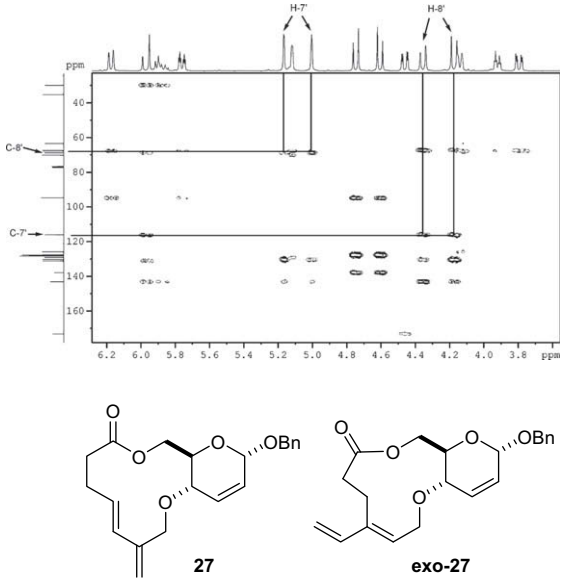


Figure 3. HMBC for compound **27**.

3. Conclusions

In conclusion, we have demonstrated the synthesis of versatile macrocyclic scaffolds for DOS. The 12- to 18-membered cyclic scaffolds are readily available in few steps and good overall yield from commercially available building blocks. In all cases, the enyne RCM of the desired product proceeded with high selectivity, leaving a core scaffold with orthogonal functional groups that effectively emerged during the build-up of the core scaffolds for further diversification.

4. Experimental section

4.1. General procedures

Solvents and reagents were used as purchased from commercial suppliers, unless otherwise noted. Dry THF was obtained via distillation over sodium using benzophenone as an indicator. Yields refer to chromatographically and spectroscopically (^{1}H NMR) homogeneous materials, unless otherwise stated. Reactions were monitored by thin-layer chromatography (TLC) carried out on Sigma–Aldrich silica gel plates (catalogue #Z193291-1PAK) using phosphomolybdic acid in absolute EtOH and heat as a developing agent. NMR spectra were recorded on either a Bruker AC 300 or DRX 400 instrument using residual undeuterated solvent as an internal reference. The following abbreviations were used to explain the multiplicities: s=singlet, d=doublet, t=triplet, q=quartet, p=pentet, m=multiplet, br=broad. Low resolution mass spectra (MS) were recorded on a Bruker Esquire 3000 (Agilent model 1100) instrument using electrospray ionization-ion trap (ESI). High resolution mass spectra (HRMS) were recorded on a Kratos MS80 RFA instrument using electron impact (EI) or on an Applied Biosystems/PE Sciex QSTAR Pulsar *i* Hybrid quadrupole time-of-flight mass spectrometer using ESI-TOF (electrospray ionization-time of flight). Optical rotations were obtained on a Rudolf Research Autopole IV at 589 nm and 22 °C.

4.2. General procedure A: glycosylation with tri-*O*-acetyl-D-glucal

A solution of tri-*O*-acetyl-D-glucal (0.1 M in DCM) stirring at 0 °C was treated, sequentially, with the corresponding alcohol (1.1 equiv), and $BF_3 \cdot OEt_2$ (0.1 equiv), in a modification of conditions set out by Ferrier

and Prasad.[8] After 2 h, the reaction mixture was allowed to warm to room temperature and stirred for an additional 2 h. The reaction was quenched with saturated aqueous $NaHCO_3$. The organic layer was separated from the aqueous layer, then washed with saturated aqueous $NaHCO_3$, saturated aqueous NH_4Cl, and dried with $MgSO_4$. The solvent was removed under reduced pressure to provide an orange tinted oil, which was purified by flash chromatography (5:1 hexane/EtOAc) or recrystallized from absolute EtOH to yield the corresponding product.

4.3. General procedure B: esterification

A solution of the alcohol (45 mM in CH_3CN), the carboxylic acid (2 equiv), DIEA (2 equiv), and DMAP (0.1 equiv) was treated with EDC·HCl (2 equiv). After 4 h, the solvent was removed under reduced pressure. The resulting residue was dissolved in DCM (5 mL), transferred to a separatory funnel, and diluted with EtOAc (50 mL). The organic fraction was washed with 1 N HCl, saturated aqueous $NaHCO_3$, dried with $MgSO_4$, filtered, and the solvent was removed in vacuo. The resulting oil was purified by flash chromatography (20:1→15:1 Hexanes/EtOAc) to yield the corresponding product.

4.4. General procedure C: ring-closing metathesis

The conditions set out here are a modification of the ring-closing conditions described by Hansen and Lee.[7a] Ethylene was bubbled through a solution of the monocyclic enyne precursor (1 mM in DCM) and second generation Grubbs' catalyst (20 mol %) for 30 min, then set to reflux under an ethylene atmosphere overnight. The solution was concentrated in vacuo and then purified by flash chromatography (toluene, then 22:1→16:1 Hexanes/EtOAc) to yield the corresponding acyclic diene (where applicable) and the cyclized product(s).

4.5. Synthetic details

4.5.1. Macrocyclic precursors. The procedures and characterization of the macrocyclic precursors is described in Supplementary data.

4.5.2. Compound ***25***. Benzyl 4-*O*-(4-pent-4-enoyl)-6-*O*-propargyl-2,3-dideoxy-α-D-*erythro*-hex-2-enpyranoside (**11**) (427 mg, 1.17 mmol) was treated according to general procedure C to provide a 20:1 mixture of 12- and 11-membered bicyclic rings, respectively, which was not separable by chromatography (223 mg, 52%) and a pure fraction of the 12-membered bicyclic ring **25** (56 mg, 13%); $[\alpha]_D$ +50 (*c* 0.032, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25–7.36 (m, 5H; Ph), 5.79–6.00 (m, 3H; H-3, H-4′, H-5′), 5.73 (dt, 1H, *J*=10.2, 2.4 Hz; H-2), 5.40 (br d, 1H, *J*=9.7 Hz; H-4), 5.15 (s, 1H; H-3′), 5.13 (br s, 1H; H-1), 4.95 (s, 1H; H-3′), 4.77 (d, 1H, *J*=11.9 Hz; Bn), 4.59 (d, 1H, *J*=11.9 Hz; Bn), 4.34 (d, 1H, *J*=12.8 Hz; H-1′), 3.95–4.03 (m, 2H; H-1′, H-5), 3.54 (dd, 1H, *J*=10.2, 2.2 Hz; H-6), 3.23 (dd, 1H, *J*=10.2, 2.0 Hz; H-6), 2.27–2.50 (m, 4H; H-6′, H-7′); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 173.2 (C-8′), 144.4 (C-2′), 137.9 (Ph), 131.1 (C-2), 130.8 (C-4′), 130.7 (C-5′), 128.3 (Ph), 128.0 (Ph), 127.9 (Ph), 127.6 (Ph), 126.6 (C-3), 114.7 (C-3′), 94.6 (C-1), 72.5 (C-1′), 70.2 (Bn), 67.8 (C-5), 66.7 (C-4), 65.6 (C-6), 35.5 (C-6′ or C-7′), 29.9 (C-6′ or C-7′). HRMS (ESI-TOF) calcd for $C_{21}H_{24}O_5$ [M+K] 395.1261, found 395.1187, calcd for $C_{21}H_{24}O_5$ [M+Na] 379.1522, found 379.1429, calcd for $C_{21}H_{24}O_5$ [M+NH_4] 374.1968, found 374.1911.

4.5.3. Compound ***27***. Benzyl 6-*O*-(pent-4-enoyl)-4-*O*-propargyl-2,3-dideoxy-α-D-*erythro*-hex-2-enpyranoside (**16**) (289 mg, 0.812 mmol) was cyclized by the conditions outlined in general procedure C to provide the bicyclic product as a clear oil (214 mg, 74%); $[\alpha]_D$ +82 (*c* 0.006, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25–7.36 (m, 5H; Ph), 6.16 (d, 1H, *J*=10.3 Hz; H-3), 5.96 (d, 1H, *J*=15.9 Hz; H-5′), 5.82–5.92 (m, 1H; H-4′), 5.75 (dt, 1H, *J*=10.3, 2.3 Hz; H-2), 5.2 (s, 1H; H-7′), 5.11 (br s, 1H; H-1), 4.99 (s, 1H; H-7′), 4.74 (d, 1H, *J*=12.0 Hz; Bn), 4.60 (d, 1H, *J*=12.0 Hz; Bn), 4.45 (dd, 1H, *J*=12.1, 2.4 Hz; H-6), 4.34 (d, 1H, *J*=12.3 Hz; H-8′), 4.11–4.19 (m, 2H; H-4, H-8′), 3.91 (dt, 1H, *J*=9.2, 2.4 Hz; H-5), 3.78 (dd, 1H, *J*=12.1, 2.7 Hz; H-6), 2.38–2.50 (m, 4H; H-2′, H-3′); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 173.3 (C-1′), 143.1 (C-6′), 137.9 (Ph), 131.1 (C-4′), 130.4 (C-5′), 129.1 (C-2), 128.3 (Ph), 127.8 (Ph), 127.72 (Ph), 127.68 (Ph), 127.6 (Ph), 125.8 (C-3), 116.1 (C-7′), 94.8 (C-1), 70.2 (Bn), 68.8 (C-8′), 67.8 (C-5), 67.4 (C-4), 63.4 (C-6), 35.3 (C-2′ or C-3′), 29.9 (C-2′ or C-3′). HRMS (ESI-TOF) calcd for $C_{21}H_{24}O_5$ [M+K] 395.1261, found 395.1214, calcd for $C_{21}H_{24}O_5$ [M+Na] 379.1522, found 379.1470, calcd for $C_{21}H_{24}O_5$ [M+NH_4] 374.1968, found 374.1938.

4.5.4. Compound ***28***. Benzyl 6-*O*-allyl-4-*O*-(4-pent-4-ynoyl)-2,3-dideoxy-α-D-*erythro*-hex-2-enpyranoside (**21**) (1.02 g, 2.85 mmol) was made according to general procedure C to provide the corresponding monocyclic tetraene **28-tetraene** (460 mg, 42%) and the bicyclic, ring closed product **28** (356 mg, 35%). Compound **28-tetraene**: $[\alpha]_D$ +81 (*c* 0.066, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.23–7.44 (m, 5H; Ph), 6.36 (dd, 1H, *J*=18.0, 10.8 Hz), 5.79–5.99 (m, 3H), 5.43 (br d, 1H, *J*=9.7 Hz; H-4), 4.97–5.35 (m, 7H), 4.83 (d, 1H, *J*=11.8 Hz; Bn), 4.59 (d, 1H, *J*=11.8 Hz; Bn), 3.96–4.16 (m, 3H), 3.54 (d, 2H, *J*=3.1 Hz), 2.54 (br s, 4H). HRMS (ESI-TOF) calcd for $C_{23}H_{28}O_5$ [M+K] 423.1574, found 423.1565, calcd for $C_{23}H_{28}O_5$ [M+NH_4] 402.2281, found 402.2285. Compound **28**: $[\alpha]_D$ +187 (*c* 0.057, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25–7.41 (m, 5H; Ph), 6.17 (d, 1H, *J*=16.1 Hz; H-3′), 5.19 (d, 1H, *J*=10.2 Hz; H-3), 5.72 (dt, 1H, *J*=10.2, 2.3 Hz; H-2), 5.54 (br d, 1H, *J*=9.8 Hz; H-4), 5.42 (ddd, 1H, *J*=16.1, 10.1, 4.3 Hz; H-2′), 5.13 (br s, 1H; H-1), 5.06 (s, 1H; H-5′), 5.03 (s, 1H; H-5′), 4.76 (d, 1H, *J*=11.9 Hz; Bn), 4.60 (d, 1H, *J*=11.9 Hz; Bn), 4.34 (dd, 1H, *J*=12.0, 4.2 Hz; H-1′), 3.89 (d, 1H, *J*=9.7 Hz; H-5), 3.48–3.61 (m, 3H; H-1′, H-6), 2.89 (dd, 1H, *J*=12.5, 11.4 Hz; H-6′), 2.84 (dd, 1H, *J*=12.9, 9.3 Hz; H-7′), 2.53 (dd, 1H, *J*=13.9, 9.3 Hz; H-6′), 2.11 (dd, 1H, *J*=12.0, 11.9 Hz; H-7′); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 174.8 (C-8′), 145.9 (C-4′), 137.7 (Ph), 137.5 (C-3′), 130.4 (C-2), 128.1 (Ph), 127.7 (Ph), 127.4 (Ph), 126.6 (C-3), 125.9 (C-2′), 118.3 (C-5′), 94.3 (C-1), 70.7 (C-1′), 70.1 (Bn), 68.4 (C-5), 65.1 (C-4), 62.7 (C-6), 35.7 (C-7′), 29.8 (C-6′). MS (ESI; *m*/*z*) 379 [M+Na]; MS/MS (*m*/*z*) 321 [M+Na−C_3H_4O], 271 [M+Na−BnOH], 239 [M+Na−$C_7H_8O_3$]; HRMS (ESI-TOF) calcd for $C_{21}H_{24}O_5$ [M+K] 395.1261, found 395.1189, calcd for $C_{21}H_{24}O_5$ [M+Na] 379.1522, found 379.1430, calcd for $C_{21}H_{24}O_5$ [M+NH_4] 374.1968, found 374.1910.

4.5.5. Compound ***29***. Benzyl 4-*O*-allyl-6-*O*-(4-pent-4-ynoyl)-2,3-dideoxy-α-D-*erythro*-hex-2-enpyranoside (**22**) (347 mg, 0.974 mmol) was treated according to general procedure C to yield the corresponding monocyclic tetraene **29-tetraene** (46 mg, 12%) and the bicyclic product **29** (226 mg, 65%). Compound **29-tetraene**: $[\alpha]_D$ +65 (*c* 0.0074, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24–7.44 (m, 5H; Ph), 6.37 (dd, 1H, *J*=17.4, 10.8 Hz), 6.08 (d, 1H, *J*=10.3 Hz; H-3), 5.76–5.98 (m, 2H), 5.15–5.36 (m, 3H), 4.98–5.14 (m, 4H), 4.82 (d, 1H, *J*=11.8 Hz; Bn), 4.58 (d, 1H, *J*=11.8 Hz; Bn), 4.33 (d, 2H, *J*=3.6 Hz; H-6), 3.90–4.20 (m, 4H), 2.59 (br s, 4H). HRMS (ESI-TOF) calcd for $C_{23}H_{28}O_5$ [M+K] 423.1574, found 423.1586, calcd for $C_{23}H_{28}O_5$ [M+NH_4] 402.2281, found 402.2303. Compound **29**: $[\alpha]_D$ +88 (*c* 0.014, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25–7.41 (m, 5H; Ph), 6.19 (d, 1H, *J*=16.1 Hz; H-6′), 6.04 (d, 1H, *J*=10.2 Hz; H-3), 5.73 (dt, 1H, *J*=10.2, 2.3 Hz; H-2), 5.39 (ddd, 1H, *J*=16.0, 10.2, 4.0 Hz; H-7′), 5.13 (br s, 1H; H-1), 5.06 (s, 1H; H-5′), 5.01 (s, 1H; H-5′), 4.97 (dd, 1H, *J*=12.6, 2.4 Hz; H-6), 4.74 (d, 1H, *J*=12.1 Hz; Bn), 4.62 (d, 1H, *J*=12.1 Hz; Bn), 4.30 (dd, 1H, *J*=12.3, 3.2 Hz; H-8′), 4.18 (br d, 1H, *J*=9.5 Hz; H-4), 3.87 (br d, 1H, *J*=9.5 Hz; H-5), 3.75 (dd, 1H, *J*=12.3, 10.3 Hz; H-8′), 3.56 (d, 1H, *J*=12.5 Hz; H-6), 2.85 (dd, 1H, *J*=13.8, 10.9 Hz; H-3′), 2.65 (dd, 1H, *J*=13.1, 9.7 Hz; H-2′), 2.55 (dd, 1H, *J*=13.9, 9.7 Hz; H-3′), 2.23 (dd, 1H, *J*=12.5, 10.6 Hz; H-2′); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 175.2 (C-1′), 146.0 (C-4′), 137.9 (Ph), 137.6 (C-6′), 131.8 (C-2), 128.3 (Ph), 128.2 (Ph), 127.64 (Ph), 127.58 (Ph), 127.5 (Ph), 125.9 (C-7′), 125.5 (C-3), 118.4 (C-5′), 94.8 (C-1), 70.2 (Bn), 69.0 (C-8′), 68.1 (C-5), 64.1 (C-4), 62.2 (C-6), 35.5 (C-2′), 29.7 (C-3′).

HRMS (ESI-TOF) calcd for $C_{21}H_{24}O_5$ [M+K] 395.1261, found 395.1200, calcd for $C_{21}H_{24}O_5$ [M+Na] 379.1522, found 379.1452, calcd for $C_{21}H_{24}O_5$ [M+NH_4] 374.1968, found 374.1929.

*4.5.6. Cyclization of compound **23**.* Benzyl 6-*O*-(2-butynyl)-4-*O*-(4-pent-4-enoyl)-2,3-dideoxy-α-D-*erythro*-hex-2-enpyranoside (**23**) (490 mg, 1.32 mmol) was subjected to cyclization conditions outlined by general procedure C to yield the corresponding monocyclic tetraene **23x** (252 mg, 41%), a 1:1 mixture of the corresponding 11- and 12-membered bicyclic rings, which could not be separated by chromatography (243 mg, 43%), and a pure fraction of the 11-membered ring **23y** (27 mg, 5%). Compound **23x**: $[\alpha]_D$ +93 (*c* 0.048, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25–7.43 (m, 5H; Ph), 5.74–5.95 (m, 3H), 5.39 (br d, 1H, *J*=9.7 Hz; H-4), 4.98–5.32 (m, 7H), 4.84 (d, 1H, *J*=11.8 Hz; Bn), 4.61 (d, 1H, *J*=11.8 Hz; Bn), 4.35 (d, 1H, *J*=12.8 Hz), 4.10–4.25 (m, 2H), 3.50–3.63 (m, 2H; H-6), 2.32–2.47 (m, 4H), 1.93 (s, 3H; Me). HRMS (ESI-TOF) calcd for $C_{24}H_{30}O_5$ [M+K] 437.1730, found 437.1747, calcd for $C_{24}H_{30}O_5$ [M+NH_4] 416.2437, found 416.2441. Compound **23y**: (27 mg, 5%); $[\alpha]_D$ +125 (*c* 0.011, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25–7.39 (m, 5H; Ph), 6.05 (d, 1H, *J*=10.2 Hz; H-3), 5.76 (dt, 1H, *J*=10.2, 2.0 Hz; H-2), 5.58 (dd, 1H, *J*=11.2, 4.3; H-6′), 5.20 (d, 1H, *J*=9.1 Hz; H-4), 5.14 (br s, 1H; H-1), 4.98 (s, 1H; H-4′), 4.81 (d, 1H, *J*=11.9 Hz; Bn), 4.77 (s, 1H; H-4′), 4.62 (d, 1H, *J*=11.9 Hz; Bn), 4.13 (d, 1H, *J*=12.3 Hz; H-1′), 3.96 (br d, 1H, *J*=9.8 Hz; H-5), 3.78–3.85 (m, 2H; H-6), 3.75 (d, 1H, *J*=12.2 Hz; H-1′), 2.83–2.98 (m, 1H), 2.33–2.49 (m, 3H), 1.91 (s, 3H; H-5′); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 173.6 (C-9′), 142.9 (C-2′ or C-3′), 141.8 (C-2′ or C-3′), 137.9 (Ph), 130.8 (C-2), 129.3 (C-6′), 128.4 (Ph), 128.0 (Ph), 127.7 (Ph), 126.9 (C-3), 115.5 (C-4′), 94.5 (C-1), 74.3 (C-1′), 70.2 (Bn), 69.2 (C-5), 67.4 (C-6), 66.6 (C-4), 35.5, 26.6, 22.4 (C-5′). HRMS (ESI-TOF) calcd for $C_{22}H_{26}O_5$ [M+K] 409.1417, found 409.1347, calcd for $C_{22}H_{26}O_5$ [M+Na] 393.1678, found 393.1622, calcd for $C_{22}H_{26}O_5$ [M+NH_4] 388.2124, found 388.2066.

*4.5.7. Cyclization of compound **24**.* Benzyl 4-*O*-(2-butynyl)-6-*O*-(pent-4-enoyl)-2,3-dideoxy-α-D-*erythro*-hex-2-enpyranoside (**24**) (332 mg, 0.895 mmol) was treated according to general procedure C to provide the monocyclic tetraene **24x** (43 mg, 12%), a 1:1 mixture of 11- and 12-membered bicyclic rings, which could not be separated by chromatography (74 mg, 22%), and a pure fraction of the bicyclic 11-membered ring **24y** (21 mg, 6%). Compound **24x**: $[\alpha]_D$ +66 (*c* 0.011, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25–7.41 (m, 5H; Ph), 6.10 (br d, 1H, *J*=10.3 Hz; H-3), 5.76–5.92 (m, 2H), 5.27 (d, 2H, *J*=8.2 Hz), 4.96–5.18 (m, 5H), 4.82 (d, 1H, *J*=11.8 Hz; Bn), 4.58 (d, 1H, *J*=11.8 Hz; Bn), 4.35 (d, 1H, *J*=12.3 Hz), 4.23–4.32 (m, 2H), 4.18 (d, 1H, *J*=12.3 Hz), 4.05–4.13 (m, 1H; H-5), 3.97 (dd, 1H, *J*=9.2, 1.0 Hz; H-4), 2.34–2.53 (m, 4H), 1.93 (s, 3H; Me). HRMS (ESI-TOF) calcd for $C_{24}H_{30}O_5$ [M+K] 437.1730, found 437.1710, calcd for $C_{24}H_{30}O_5$ [M+NH_4] 416.2437, found 416.2404. Compound **24y**: $[\alpha]_D$ +144 (*c* 0.01, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26–7.39 (m, 5H; Ph), 6.09 (d, H, *J*=10.3 Hz; H-3), 5.85 (t, 1H, *J*=8.2 Hz; H-6′), 5.79 (dt, 1H, *J*=10.3, 2.0 Hz; H-2), 5.14 (s, 1H; H-4′), 5.04 (br s, 1H; H-1), 4.98 (s, 1H; H-4′), 4.75 (d, 1H, *J*=12.0 Hz; Bn), 4.59 (d, 1H, *J*=12.0 Hz; Bn), 4.38 (d, 1H, *J*=10.7 Hz; H-1′), 4.09–4.27 (m, 4H; H-1′, H-5, H-6), 4.01 (br d, 1H, *J*=8.4 Hz; H-4), 2.61–2.76 (m, 1H; H-7′ or H-8′), 2.38–2.60 (m, 3H; H-7′, H-8′), 1.90 (s, 3H; H-5′); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 172.0 (C-9′), 142.7 (C-2′ or C-3′), 138.4 (C-2′ or C-3′), 137.9 (Ph), 130.7 (C-6′), 130.4 (C-2), 128.4 (Ph), 128.2 (Ph), 127.9 (Ph), 127.6 (Ph), 126.1 (C-3), 112.8 (C-4′), 93.6 (C-1), 73.3 (C-4), 70.2 (Bn), 65.3 (C-5), 64.9 (C-6), 63.4 (C-1′), 34.6 (C-7′ or C-8′), 24.6 (C-7′ or C-8′), 21.1 (C-5′). HRMS (ESI-TOF) calcd for $C_{22}H_{26}O_5$ [M+K] 409.1417, found 409.1349, calcd for $C_{22}H_{26}O_5$ [M+Na] 393.1678, found 393.1621, calcd for $C_{22}H_{26}O_5$ [M+NH_4] 388.2124, found 388.2070.

*4.5.8. Compound **30**.* Benzyl 4-*O*-(hex-5-enoyl)-6-*O*-propargyl-2,3-dideoxy-α-D-*erythro*-hex-2-enpyranoside (**12**) (222 mg, 0.599 mmol) was subjected to the cyclization conditions outlined by general procedure C to provide two fractions of the title compound. The first fraction was the title compound at 90% purity by NMR and the impurity was not separable from the title compound by chromatography (140 mg, 63%). The second fraction was pure title compound (19 mg, 9%); $[\alpha]_D$ +128 (*c* 0.006, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25–7.48 (m, 5H; Ph), 6.02 (d, 1H, *J*=15.7 Hz; H-4′), 5.86–5.91 (m, 2H; H-3, H-5′), 5.75 (dt, 1H, *J*=10.2, 2.4 Hz; H-2), 5.62 (dd, 1H, *J*=9.7, 1.6 Hz; H-4), 5.14 (br s, 2H; H-1, H-3′), 5.02 (s, 1H; H-3′), 4.79 (d, 1H, *J*=11.9 Hz; Bn), 4.61 (d, 1H, *J*=11.9 Hz; Bn), 4.44 (d, 1H, *J*=12.1 Hz; H-1′), 4.02 (dt, 1H, *J*=9.7, 2.5 Hz; H-5), 3.96 (d, 1H, *J*=12.2 Hz; H-1′), 3.61 (dd, 1H, *J*=10.3, 3.1 Hz; H-6), 3.33 (dd, 1H, *J*=10.3, 2.0 Hz; H-6), 2.01–2.48 (m, 5H), 1.71–1.82 (m, 1H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 173.4 (C-9′), 142.5 (C-2′), 137.9 (Ph), 131.2 (C-2), 130.7 (C-4′), 130.5 (C-5′), 128.4 (Ph), 127.9 (Ph), 127.8 (Ph), 127.7 (Ph), 126.6 (C-3), 116.6 (C-3′), 94.5 (C-1), 72.5 (C-1′), 70.2 (Bn), 67.9 (C-5), 66.8 (C-6), 65.8 (C-4), 32.9, 32.4, 22.9. HRMS (ESI-TOF) calcd for $C_{22}H_{26}O_5$ [M+K] 409.1417, found 409.1346, calcd for $C_{22}H_{26}O_5$ [M+Na] 393.1678, found 393.1612, calcd for $C_{22}H_{26}O_5$ [M+NH_4] 388.2124, found 388.2079.

*4.5.9. Compound **31**.* Benzyl 4-*O*-(hept-6-enoyl)-6-*O*-propargyl-2,3-dideoxy-α-D-*erythro*-hex-2-enpyranoside (**13**) (271 mg, 0.704 mmol) was cyclized according to general procedure C to produce two fractions of the title compound. The first fraction was 90% pure by NMR and the title compound was not separable from the impurity by chromatography (105 mg, 39%); the second fraction was pure title compound (90 mg, 33%); $[\alpha]_D$ +187 (*c* 0.034, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25–7.40 (m, 5H; Ph), 6.10 (d, 1H, *J*=10.2 Hz; H-3), 6.03 (d, 1H, *J*=16.0 Hz; H-4′), 5.9 (ddd, 1H, *J*=15.8, 9.1, 4.9 Hz; H-5′), 5.78 (dt, 1H, *J*=10.2, 2.4 Hz; H-2), 5.32 (dd, 1H, *J*=9.9, 1.6 Hz; H-4), 5.17 (br s, 1H; H-1), 5.10 (s, 1H; H-3′), 5.05 (s, 1H; H-3′), 4.79 (d, 1H, *J*=11.9 Hz; Bn), 4.63 (d, 1H, *J*=11.9 Hz; Bn), 4.61 (d, 1H, *J*=11.9 Hz; H-1′), 4.01 (dt, 1H, *J*=9.9, 2.3 Hz; H-5), 3.96 (d, 1H, *J*=12.1 Hz; H-1′), 3.64 (dd, 1H, *J*=10.5, 2.6 Hz; H-6), 3.15 (dd, 1H, *J*=10.5, 2.0 Hz; H-6), 2.47 (ddd, 1H, *J*=13.6, 7.0, 3.0 Hz), 2.31–2.41 (m, 1H), 2.15 (dt, 1H, *J*=10.7, 3.9 Hz), 1.85–1.95 (m, 1H), 1.55–1.77 (m, 3H), 1.38–1.50 (m, 1H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 173.2 (C-10′), 142.2 (C-2′), 138.0 (Ph), 133.0 (C-5′), 130.9 (C-2), 129.8 (C-4′), 128.4 (Ph), 127.9 (Ph), 127.7 (Ph), 126.8 (C-3), 117.4 (C-3′), 94.7 (C-1), 72.9 (C-1′), 70.4 (Bn), 67.9 (C-5), 66.3 (C-4 or C-6), 66.2 (C-4 or C-6), 34.7, 31.6, 26.2, 23.1. HRMS (ESI-TOF) calcd for $C_{23}H_{28}O_5$ [M+K] 423.1574, found 423.1494, calcd for $C_{23}H_{28}O_5$ [M+Na] 407.1836, found 407.1751, calcd for $C_{23}H_{28}O_5$ [M+NH_4] 402.2281, found 402.2233.

*4.5.10. Compound **32**.* Benzyl 4-*O*-(non-8-enoyl)-6-*O*-propargyl-2,3-dideoxy-α-D-*erythro*-hex-2-enpyranoside (**14**) (430 mg, 1.04 mmol) was treated according to general procedure C to produce the corresponding monocyclic tetraene **32-tetraene** (223 mg, 49%) and the bicyclic compound **32** (147 mg, 34%). Compound **32-tetraene**: $[\alpha]_D$ +91 (*c* 0.047, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.24–7.46 (m, 5H; Ph), 6.37 (dd, 1H, *J*=17.9, 10.8 Hz), 5.73–5.94 (m, 3H), 5.24–5.45 (m, 3H), 4.90–5.23 (m, 5H), 4.84 (d, 1H, *J*=11.8 Hz; Bn), 4.61 (d, 1H, *J*=11.8 Hz; Bn), 4.33 (d, 1H, *J*=12.8 Hz), 4.10–4.23 (m, 2H), 3.50–3.64 (m, 2H), 2.31 (t, 2H, *J*=7.2 Hz), 2.05 (q, 2H, *J*=7.2 Hz), 1.56–1.70 (m, 2H), 1.26–1.50 (m, 6H). HRMS (ESI-TOF) calcd for $C_{27}H_{36}O_5$ [M+K] 479.2200, found 479.2212, calcd for $C_{27}H_{36}O_5$ [M+NH_4] 458.2907, found 458.2901. Compound **32**: $[\alpha]_D$=+114 (*c* 0.022, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28–7.40 (m, 5H; Ph), 5.92–6.06 (m, 3H; H-3, H-4′, H-5′), 5.82 (dt, 1H, *J*=10.2, 2.6 Hz; H-2), 5.44 (dd, 1H, *J*=9.8, 1.5 Hz; H-4), 5.17 (br s, 1H; H-1), 5.14 (d, 1H, *J*=1.7 Hz; H-3′), 5.03 (br s, 1H; H-3′), 4.81 (d, 1H, *J*=11.9 Hz; Bn), 4.63 (d, 1H, *J*=11.9 Hz; Bn), 4.43 (d, 1H, *J*=11.9 Hz; H-1′), 3.95–4.06 (m, 2H; H-1′, H-5), 3.59 (dd, 1H, *J*=10.8, 3.4 Hz; H-6), 3.24 (dd, 1H, *J*=10.8, 2.0 Hz; H-6), 2.06–2.46 (m, 4H), 1.75–1.92 (m, 1H), 1.37–1.64 (m, 4H), 1.08–1.37 (m, 3H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 173.1 (C-12′), 142.1 (C-2′), 138.0 (Ph), 132.1 (C-2, C-4′, or C-

5′), 129.8 (C-2, C-4′, or C-5′), 129.6 (C-2, C-4′, or C-5′), 129.5 (Ph), 128.3 (Ph), 128.1 (Ph), 128.0 (Ph), 127.6 (Ph), 127.4 (C-3), 116.4 (C-3′), 94.2 (C-1), 73.8 (C-1′), 70.3 (Bn), 68.0 (C-5), 67.3 (C-6), 65.3 (C-4), 33.0, 31.8, 28.1, 27.8, 26.2, 23.1. MS (ESI; *m*/*z*) 435 [M+Na]; MS/MS (*m*/*z*) 435 [M+Na], 327 [M+Na−BnOH]; HRMS (ESI-TOF) calcd for $C_{25}H_{32}O_5$ [M+K] 451.1887, found 451.1809, calcd for $C_{25}H_{32}O_5$ [M+Na] 435.2148, found 435.2074, calcd for $C_{25}H_{32}O_5$ [M+NH_4] 430.2594, found 430.2521.

4.5.11. Compound ***33***. Benzyl 6-*O*-propargyl-4-*O*-(undec-10-enoyl)-2,3-dideoxy-α-D-*erythro*-hex-2-enpyranoside (**15**) (281 mg, 0.637 mmol) was cyclized according to general procedure C to provide the product as a clear oil (152 mg, 54%); $[\alpha]_D$ +61 (*c* 0.034, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24–7.44 (m, 5H; Ph), 6.05 (d, 1H, *J*=15.9 Hz; H-4′), 5.82–5.92 (m, 3H; H-2, H-3, H-5′), 5.37 (br d, 1H, *J*=9.6 Hz; H-4), 5.14 (s, 1H; H-3′), 5.09 (br s, 2H; H-1, H-3′), 4.87 (d, 1H, *J*=11.6 Hz; Bn), 4.62 (d, 1H, *J*=11.6 Hz; Bn), 4.36 (d, 1H, *J*=12.3 Hz; H-1′), 4.24 (d, 1H, *J*=12.3 Hz; H-1′), 4.19 (ddd, 1H, *J*=9.6, 6.2, 2.0 Hz; H-5), 3.56 (dd, 1H, *J*=11.8, 2.1 Hz; H-6), 3.48 (dd, 1H, *J*=11.8, 6.3 Hz; H-6), 2.26–2.42 (m, 2H), 2.07–2.24 (m, 2H), 1.14–1.80 (m, 14H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 173.1 (C-14′), 142.4 (C-2′), 137.7 (Ph), 132.5 (C-3 or C-5′), 129.8 (C-4′), 129.6 (C-3 or C-5′), 128.3 (C-2 or Ph), 128.2 (C-2 or Ph), 127.9 (C-2 or Ph), 127.7 (C-2 or Ph), 116.0 (C-3′), 93.3 (C-1), 73.1 (C-1′), 70.1 (Bn), 69.1 (C-5), 68.1 (C-6), 65.3, 32.1, 28.1, 28.0, 27.9, 27.8, 26.5, 24.9. HRMS (ESI-TOF) calcd for $C_{27}H_{36}O_5$ [M+K] 479.2200, found 479.2156, calcd for $C_{27}H_{36}O_5$ [M+Na] 463.2461, found 463.2406, calcd for $C_{27}H_{36}O_5$ [M+NH_4] 458.2907, found 458.2854.

4.5.12. Compound ***34***. Benzyl 6-*O*-(hex-5-enoyl)-4-*O*-propargyl-2,3-dideoxy-α-D-*erythro*-hex-2-enpyranoside (**17**) (260 mg, 0.703 mmol) was subjected to the conditions outlined in general procedure C to yield the corresponding monocyclic tetraene **34-tetraene** (114 mg, 41%) and the ring closed bicyclic product **34** (94 mg, 36%). Compound **34-tetraene**: $[\alpha]_D$ +60 (*c* 0.014, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26–7.40 (m, 5H; Ph), 6.36 (dd, 1H, *J*=17.9, 11.3 Hz), 6.11 (d, 1H, *J*=10.3 Hz; H-3), 5.67–5.86 (m, 2H), 4.94–5.39 (m, 7H), 4.82 (d, 1H, *J*=11.8 Hz; Bn), 4.58 (d, 1H, *J*=11.8 Hz; Bn), 3.88–4.38 (m, 6H), 2.38 (t, 2H, *J*=7.2 Hz), 2.11 (q, 2H, *J*=7.2 Hz), 1.76 (p, 2H, *J*=7.2 Hz). HRMS (ESI-TOF) calcd for $C_{24}H_{30}O_5$ [M+K] 437.1730, found 437.1735, calcd for $C_{24}H_{30}O_5$ [M+NH_4] 416.2437, found 416.2428. Compound **34**: $[\alpha]_D$ +120 (*c* 0.02, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26–7.38 (m, 5H; Ph), 6.20 (d, 1H, *J*=10.3 Hz; H-2), 5.98 (d, 1H, *J*=15.8 Hz; H-6′), 5.89 (dt, 1H, *J*=15.7, 7.7 Hz; H-5′), 5.77 (dt, 1H, *J*=10.3, 2.00 Hz; H-3), 5.24 (s, 1H; H-8′), 5.14 (br s, 1H; H-1), 5.01 (s, 1H; H-8′), 4.76 (d, 1H, *J*=12.0 Hz; Bn), 4.52–4.67 (m, 2H; Bn, H-6), 4.29 (d, 1H, *J*=12.4 Hz; H-9′), 4.19 (d, 1H, *J*=9.2 Hz; H-4), 4.12 (d, 1H, *J*=12.4 Hz; H-9′), 3.93 (br d, 1H, *J*=9.2 Hz; H-5), 3.78 (br d, 1H, *J*=12.2 Hz; H-6), 2.17–2.48 (m, 4H), 1.93–2.09 (m, 1H), 1.76–1.90 (m, 1H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 173.6 (C-1′), 141.8 (C-7′), 137.9 (Ph), 130.6 (C-5′), 130.1 (C-6′), 129.7 (C-2), 128.3 (Ph), 128.1 (Ph), 127.7 (Ph), 127.6 (Ph), 126.0 (C-3), 116.1 (C-8′), 94.8 (C-1), 70.2 (Bn), 69.2 (C-9′), 68.0 (C-5), 67.6 (C-4), 63.1 (C-6), 32.9, 31.9, 22.9. HRMS (ESI-TOF) calcd for $C_{22}H_{26}O_5$ [M+K] 409.1417, found 409.1342, calcd for $C_{22}H_{26}O_5$ [M+Na] 393.1678, found 393.1620, calcd for $C_{22}H_{26}O_5$ [M+NH_4] 388.2124, found 388.2073.

4.5.13. Compound ***35***. Benzyl 6-*O*-(hept-6-enoyl)-4-*O*-propargyl-2,3-dideoxy-α-D-*erythro*-hex-2-enpyranoside (**18**) (270 mg, 0.702 mmol) was used to synthesize the bicyclic product by general procedure C (184 mg, 68%); $[\alpha]_D$ +180 (*c* 0.018, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26–7.36 (m, 5H; Ph), 6.34 (d, 1H, *J*=10.4 Hz; H-3), 6.08 (d, 1H, *J*=15.9 Hz; H-7′), 5.89 (ddd, 1H, *J*=15.7, 8.2, 5.8 Hz; H-6′), 5.80 (dt, 1H, *J*=10.4, 2.4 Hz; H-2), 5.16 (s, 1H; H-9′), 5.13 (br s, 1H; H-1), 5.10 (s, 1H; H-9′), 4.76 (d, 1H, *J*=11.9 Hz; Bn), 4.60 (d, 1H, 11.9 Hz; Bn), 4.46 (d, 1H, *J*=11.8 Hz; H-10′), 4.30 (dd, 1H, *J*=9.3, 1.3 Hz; H-4), 4.25 (d, 1H, *J*=11.9 Hz; H-10′), 4.20 (br s, 2H; H-6), 3.98 (dt, 1H, *J*=9.3, 2.06 Hz; H-5), 2.63 (ddd, 1H, *J*=14.7, 6.4, 3.3 Hz), 2.20–2.34 (m, 2H), 1.82–2.03 (m, 2H), 1.56–1.77 (m, 2H), 1.95–1.30 (m, 1H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 173.6 (C-1′), 141.6 (C-8′), 137.9 (Ph), 132.0 (C-6′), 130.2 (C-7′), 129.0 (C-2), 128.4 (Ph), 127.9 (Ph), 127.7 (Ph), 126.5 (C-3), 118.5 (C-9′), 94.8 (C-1), 70.2 (Bn), 68.3 (C-10′), 68.1 (C-5), 67.3 (C-4), 63.1 (C-6), 34.8, 31.3, 26.9, 22.6. MS (ESI; *m*/*z*) 407 [M+Na]; MS/MS (*m*/*z*) 316 [M+Na−C_7H_7], 287 [M+Na−C_8H_8O]; HRMS (ESI-TOF) calcd for $C_{23}H_{28}O_5$ [M+K] 423.1574, found 423.1522, calcd for $C_{23}H_{28}O_5$ [M+Na] 407.1835, found 407.1778, calcd for $C_{23}H_{28}O_5$ [M+NH_4] 402.2281, found 402.2235.

4.5.14. Compound ***36***. Benzyl 6-*O*-(non-8-enoyl)-4-*O*-propargyl-2,3-dideoxy-α-D-*erythro*-hex-2-enpyranoside (**19**) (293 mg, 0.712 mmol) was treated according to general procedure C to provide the product as a clear oil (179 mg, 61%); $[\alpha]_D$ +116 (*c* 0.057, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25–7.40 (m, 5H; Ph), 6.20 (d, 1H, *J*=10.3 Hz; H-3), 6.07 (d, 1H, *J*=15.9 Hz; H-9′), 5.80–5.87 (m, 2H; H-2, H-8′), 5.13 (s, 1H; H-1 or H-11′), 5.11 (br s, 1H; H-1 or H-11′), 5.07 (s, 1H; H-1 or H-11′), 4.79 (d, 1H, *J*=11.8 Hz; Bn), 4.59 (d, 1H, *J*=11.8 Hz; Bn), 4.35 (d, 1H, *J*=11.5 Hz; H-12′), 4.23 (dd, 1H, *J*=12.1, 1.5 Hz; H-6), 4.17 (dd, 1H, *J*=12.1, 3.5 Hz; H-6), 4.02–4.13 (m, 3H; H-4, H-5, H-12′), 2.33–2.42 (m, 2H), 2.17–2.29 (m, 1H), 2.03–2.11 (m, 1H), 1.79–1.93 (m, 1H), 1.59–1.72 (m, 1H), 1.11–1.53 (m, 6H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 174.3 (C-1′), 141.8 (C-10′), 137.9 (Ph), 132.0 (C-3 or C-8′), 130.0 (C-9′), 129.6 (C-2), 128.3 (Ph), 127.9 (Ph), 127.6 (Ph), 126.8 (C-3 or C-8′), 117.2 (C11′), 94.0 (C-1), 70.1 (C-12′), 69.4 (Bn), 69.1 (C-4 or C-5), 68.1 (C-4 or C-5), 64.0 (C-6), 33.5, 31.6, 28.2, 27.9, 26.1, 24.6. MS (ESI; *m*/*z*) 435 [M+Na]; MS/MS (*m*/*z*) 435 [M+Na], 344 [M+Na−C_7H_7], 301 [M+Na−$C_9H_{10}O$]; HRMS (ESI-TOF) calcd for $C_{25}H_{32}O_5$ [M+K] 451.1887, found 451.1820, calcd for $C_{25}H_{32}O_5$ [M+Na] 435.2148, found 435.2083, calcd for $C_{25}H_{32}O_5$ [M+NH_4] 430.2594, found 430.2513.

4.5.15. Compound ***37***. Benzyl 4-*O*-propargyl-6-*O*-(undec-10-enoyl)-2,3-dideoxy-α-D-*erythro*-hex-2-enpyranoside (**20**) (304 mg, 0.690 mmol) was treated with Grubbs' second generation catalyst under the conditions outlined by general procedure C to yield the product as a clear oil (202 mg, 67%); $[\alpha]_D$ +60 (*c* 0.021, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29–7.39 (m, 5H; Ph), 6.12 (d, 1H, *J*=10.3 Hz; H-3), 6.05 (d, 1H, *J*=15.9 Hz; H-11′), 5.84 (dt, 1H, *J*=10.3, 2.6 Hz; H-2), 5.77 (dd, 1H, *J*=15.9, 7.13 Hz; H-10′), 5.06–5.12 (m, 3H; H-1, H-13′), 4.82 (d, 1H, *J*=11.7 Hz; Bn), 4.57 (d, 1H, *J*=11.7 Hz; Bn), 4.35 (dd, 1H, *J*=12.0, 5.9 Hz; H-6), 4.35 (d, 1H, *J*=12.1 Hz; H-14′), 4.17 (dd, 1H, *J*=12.0, 1.6 Hz; H-6), 4.11 (ddd, 1H, *J*=9.5, 6.0, 1.6 Hz; H-5), 4.05 (d, 1H, *J*=12.1 Hz; H-14′), 3.96 (dd, 1H, *J*=9.5, 1.4 Hz; H-4), 2.38 (t, 2H, *J*=6.5 Hz; H-2′), 2.13 (p, 2H, *J*=6.8 Hz; H-3′), 1.60–1.75 (m, 2H), 1.20–1.46 (m, 10H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 173.9 (C-1′), 142.0 (C-12′), 137.8 (Ph), 132.4 (C-10′), 130.3 (C-2), 129.8 (C-11′), 128.4 (Ph), 128.0 (Ph), 127.7 (Ph), 126.7 (C-3), 115.7 (C-13′), 93.6 (C-1), 70.1 (C-4), 69.9 (Bn), 69.6 (C-14′), 68.2 (C-5), 64.0 (C-6), 34.0 (C-2′), 32.7 (C-3′), 28.1, 27.4, 27.2, 26.9, 24.3. MS (ESI; *m*/*z*) 463 [M+Na]; MS/MS (*m*/*z*) 463 [M+Na], 372 [M+Na−C_7H_7], 355 [M+Na−BnOH]; HRMS (ESI-TOF) calcd for $C_{27}H_{36}O_5$ [M+K] 479.2200, found 479.2126, calcd for $C_{27}H_{36}O_5$ [M+Na] 463.2461, found 463.2384, calcd for $C_{27}H_{36}O_5$ [M+NH_4] 458.2907, found 458.2815.

Acknowledgements

Financial support for this project was provided by the Alberta Ingenuity Fund (New Faculty Award) and National Science and Engineering Council (Discovery Grant).

Supplementary data

Synthetic procedures and characterization data, 1D-NMR spectra, and 2D-NMR spectra used for the determination of ring sizes

are all provided. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2009.07.088.

References and notes

1. (a) Lokey, R. S. *Curr. Opin. Chem. Biol.* **2003**, *7*, 91; (b) Schreiber, S. L. *Chem. Eng. News* **2003**, *81*, 51.
2. (a) Burke, M. D.; Schreiber, S. L. *Angew. Chem., Int. Ed.* **2004**, *43*, 46; (b) Cordier, C.; Morton, D.; Murrison, S.; Nelson, A.; O'Leary-Steele. *Nat. Prod. Rep.* **2008**, *25*, 719; (c) Spandl, R. J.; Rudyk, H.; Spring, D. R. *Chem. Commun.* **2008**, 3001.
3. (a) Nielsen, T. E.; Schreiber, S. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 48; (b) Schreiber, S. L. *Nature* **2009**, *457*, 153.
4. (a) Kim, Y.-K.; Arai, M. A.; Arai, T.; Lamenzo, J. O.; Dean, E. F., III; Patterson, N.; Clemons, P. A.; Schreiber, S. L. *J. Am. Chem. Soc.* **2004**, *126*, 14740; (b) Hotha, S.; Anegundi, R. I.; Natu, A. A. *Tetrahedron Lett.* **2005**, *46*, 4585; (c) Lu, K.; Huang, M.; Xiang, Z.; Liu, Y.; Chen, J.; Yang, Z. *Org. Lett.* **2006**, *8*, 1193; (d) Rivera, D. G.; Vercillo, O. E.; Wessjohann, L. A. *Org. Biomol. Chem.* **2008**, *6*, 1787.
5. (a) Winssinger, N.; Barluenga, S. *Chem. Commun.* **2007**, 22; (b) Tietza, L. F.; Bell, H. P.; Chandrasekhar, S. *Angew. Chem., Int. Ed.* **2003**, *42*, 3996.
6. (a) Potuzak, J. S.; Moilanen, S. B.; Tan, D. S. *J. Am. Chem. Soc.* **2005**, *127*, 13796; (b) Kubota, H.; Depew, K. M.; Schreiber, S. L. *Chem. Biol.* **2002**, *9*, 265; (c) Hotha, S.; Tripathi, A. *J. Comb. Chem.* **2005**, *7*, 968; (d) Moilanen, S. B.; Tan, D. S. *Org. Biomol. Chem.* **2005**, *3*, 798; (e) Moilanen, S. B.; Potuzak, J. S.; Tan, D. S. *J. Am. Chem. Soc.* **2006**, *128*, 1792; (f) Das, I.; Pal, T. K.; Suresh, C. G.; Pathak, T. *J. Org. Chem.* **2007**, *72*, 5523; (g) Yadav, L. D.; Srivastava, V. P.; Rai, V. K.; Patel, R. *Tetrahedron* **2008**, *64*, 4246.
7. (a) Hansen, E. C.; Lee, D. S. *J. Am. Chem. Soc.* **2004**, *126*, 15074; (b) Layton, M. E.; Morales, C. A.; Shair, M. D. *J. Am. Chem. Soc.* **2002**, *124*, 773; (c) Morales, C. A.; Layton, M. E.; Shair, M. D. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 12036; (d) Hansen, E. C.; Lee, D. S. *J. Am. Chem. Soc.* **2003**, *125*, 9582; (e) Barrett, A. G. M.; Hennessy, A. J.; Vezouet, R. L.; Procopiou, P. A.; Seale, P. W.; Stefananiak, S.; Upton, R. J.; White, A. J. P.; Williams, D. J. *J. Org. Chem.* **2004**, *69*, 1028.
8. Ferrier, R. J.; Prasad, N. *J. Chem. Soc. C* **1969**, 570.
9. Chaudhary, S. K.; Hernandez, O. *Tetrahedron Lett.* **1979**, *20*, 99.
10. (a) Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18; (b) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413.
11. Mori, M.; Sakakibara, N.; Kinoshita, A. *J. Org. Chem.* **1998**, *63*, 6082.
12. By stopping the reactions prematurely, a significant amount of the corresponding trienes was isolated.
13. Substrate (1 mM), Grubb's second generation catalyst (20%), $CH_2{=}CH_2$, CH_2Cl_2.