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Graphical Abstract

Stereoselective synthesis of tetrahydropyran-tetrahydrofuran (THP-THF) core of (+)-muconin *via* Prins cyclization

J. S. Yadav,* U. V. Subba Reddy, B. V. Subba Reddy

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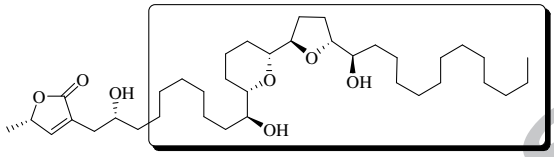

(+)-muconin

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Stereoselective synthesis of tetrahydropyran-tetrahydrofuran (THP-THF) core of (+)-muconin *via* Prins cyclization

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ABSTRACT

A stereoselective synthesis of tetrahydropyran-tetrahydrofuran (THP-THF) core **2** of (+)-muconin (**1**) has been achieved using Prins cyclization as a key step to construct tetrahydropyran moiety. Other important transformations such as Wittig olefination, Sharpless epoxidation, regio- and stereoselective *exo*-cyclization of the epoxy alcohol, titanocene induced regioselective deoxygenation of 2,3-epoxy alcohol, Grignard reaction, and Barton-McCombie reaction are successfully employed to accomplish the synthesis of THP-THF core **2**.

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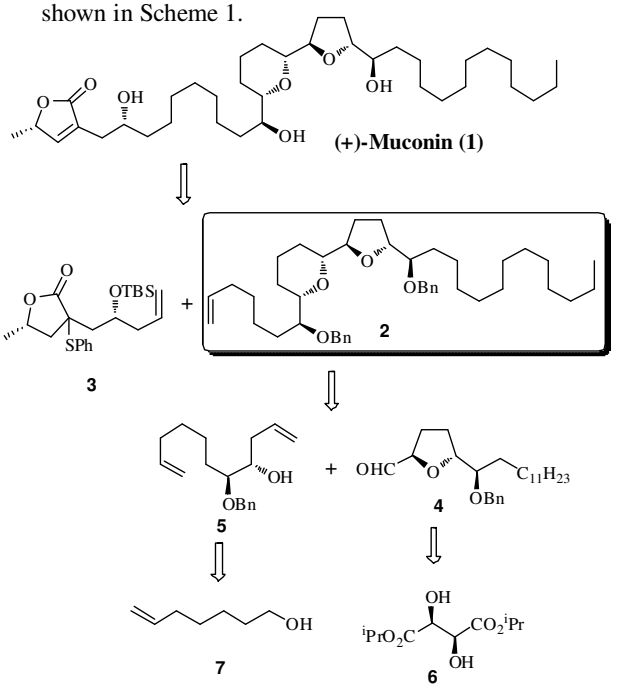
Annonaceous acetogenins are the important naturally occurring polyketides isolated from the plants of Annonaceae family. These are a novel class of rapidly emerging natural products with promising biological activities such as antitumor, antimalarial, antimicrobial, antiprotozoal and pesticidal behaviour.[1] They also act as strong insecticides, acaricides, fungicides, antiparasitics and herbicides. They are important inhibitors of complex I (NADH: ubiquinone oxidoreductase) in mammalian and insect mitochondrial electron transport systems[2] and are powerful inhibitors of NADH oxidase of the plasma membranes of cancer cells.[3] (+)-Muconin (**1**) is a rare type of non-classical acetogenin bearing THP ring along with adjacent THF ring and α,β-unsaturated γ-lactone moiety. It was isolated by McLaughlin's group in 1996 from the leaves of *Rollinia mucosa*.[4] It shows potent and selective *in vitro* cytotoxicity against PACA-2 (pancreatic cancer) and MCF-7 (breast cancer) in a panel of six human solid tumor cell lines.[4] In contrast, THP-THF core of the (+)-muconin (**1**) displays the modest cytotoxicity GI_{50} values of 90 and 85 μM against the human solid tumor cell lines A2780 and SW1573 cells respectively.[5] This clearly indicates that muconin (**1**) has tremendous biological activity. Therefore, it has become a challenge for synthetic chemists not only as a complex target but also as a promising lead molecule. Consequently, several efforts have been made on its total synthesis which resulted in six total syntheses[6] and one formal synthesis[5] of the molecule.

Following our interest on the total synthesis of natural products involving Prins cyclization,[7] we herein report a highly flexible and stereo-controlled synthesis of THP-THF core **2** of (+)-muconin (**1**) *via* Prins cyclization as a key reaction. Retrosynthetic strategy of muconin (**1**) is shown in Scheme 1.



Scheme 1. Retrosynthetic analysis of (+)-muconin (**1**)

As per our strategy, muconin (**1**) could be obtained by the coupling of butenolide fragment **3** with THP-THF core **2** through the cross-metathesis.[8] THP-THF core **2** could be prepared by the coupling of fragments **4** and **5**

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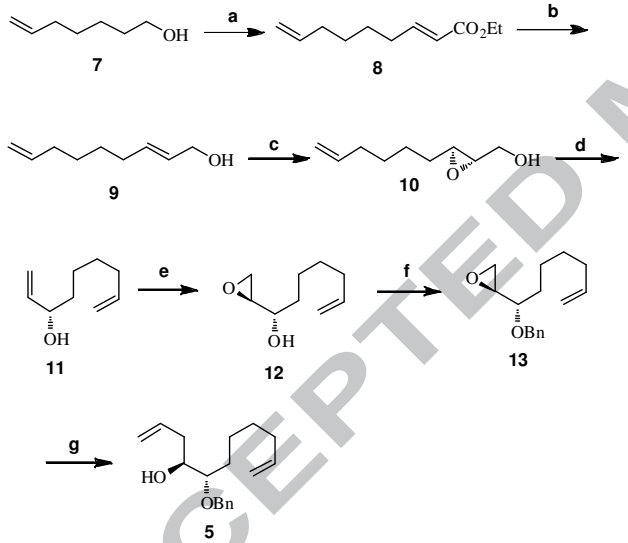
by Prins cyclization followed by deoxygenation through Barton-McCombie reaction. The homoallylic alcohol **5** could be synthesized from hepta-6-ene-1-ol **7** and aldehyde **4**, which would be derived from (-)-DIPT (**6**) using sequence of reactions such as Sharpless epoxidation, Wittig olefination and Grignard reaction.

Synthesis of homoallyl alcohol (5)

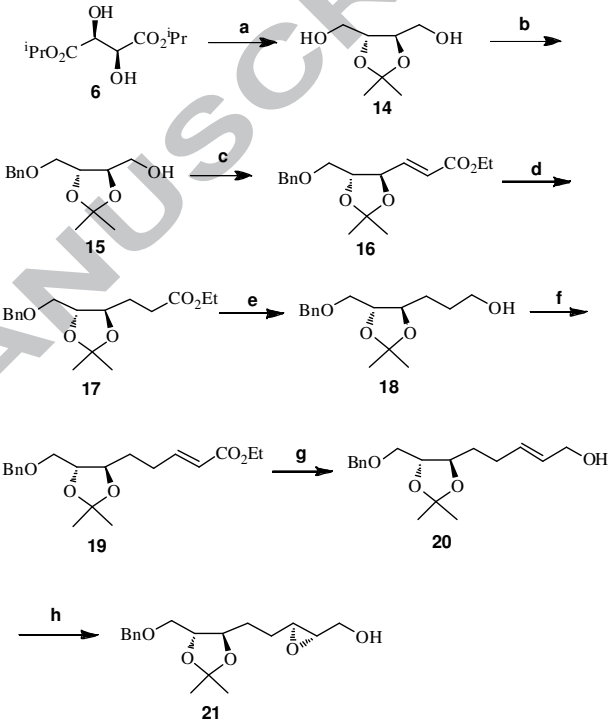
Accordingly, the hepta-6-ene-1-ol **7** was converted into aldehyde using IBX (2-Iodoxybenzoic acid)[9] in THF/DMSO. Wittig olefination[10] of the aldehyde with $Ph_3P{=}CHCO_2Et$ gave the α,β-unsaturated ester **8** in 80% yield. Reduction of the unsaturated ester **8** with DIBAL-H furnished the allylic alcohol **9** in 82% yield, which was then subjected to Sharpless asymmetric epoxidation using (+)-DET to give the chiral epoxy alcohol **10** with 96% ee in 86% yield.[11] Reductive regioselective ring opening of the epoxide **10** using our own protocol (titanium(III) in THF) furnished the allylic alcohol **11** in 88% yield.[12] Asymmetric epoxidation of the allylic alcohol **11** using (-)-DET, titanium(IV) isopropoxide and *tert*-butylhydroperoxide in anhydrous dichloromethane afforded the epoxy alcohol **12** with 92% de in 85% yield. Protection of the secondary hydroxyl group **12** with benzyl bromide in the presence of NaH gave the benzyl ether **13**. Regioselective ring opening of the terminal epoxide **13** with vinyl magnesium bromide gave the homoallylic alcohol **5** in excellent yield (Scheme 2).



Scheme 2. Reagents and conditions: a) i) IBX, THF/DMSO, 0 °C–r.t, 4h; ii) $Ph_3P{=}CHCO_2Et$, benzene r.t, 5h, 80%; b) DIBAL-H, CH_2Cl_2, -15 °C–r.t, 1h, 82%; c) (+)-DET, $Ti(O^iPr)_4$, ^{t}BuOOH, CH_2Cl_2, 4Å MS, -25 °C, 6h, 86%; d) $(C_5H_5)_2TiCl$, THF, r.t, 88%; e) (-)-DET, $Ti(O^iPr)_4$, ^{t}BuOOH, CH_2Cl_2, 4Å MS, -25 °C, 6h, 85%; f) NaH, BnBr, THF, 0 °C–r.t, 10h, 95%; g) vinyl bromide, Mg, THF, -40 °C, 1h, 80%.

Synthesis of the aldehyde fragment (4)

Our synthetic approach for the preparation of aldehyde **4** began with (-)-diisopropyl tartrate (DIPT) **6.** Protection of **6** with 2,2-dimethoxypropane using *p*-TSA followed by reduction with LAH in THF gave the diol **14** in 90% yield. Selective mono protection of the diol **14** with benzyl bromide and NaH furnished the monobenzyl ether **15** in 80% yield.[13] Oxidation of the primary alcohol **15** under Swern conditions[14] (using oxalyl chloride, DMSO and triethylamine) followed by two-carbon homologation with [(ethoxycarbonyl)methylene]triphenylphosphorane in benzene gave the (*E*)-α,β-unsaturated ester **16** in 90% overall yield for two steps. Reduction of the double bond of **16** with $NiCl_2.6H_2O$ and $NaBH_4$[15] followed by reduction of the ester with LAH gave the primary alcohol **18** in 85% yield. Conversion of the alcohol **18** into **19** was achieved in two steps *i.e.* oxidation of the primary alcohol under Swern conditions followed by C2-Wittig olefination. Reduction of the ester **19** with DIBAL-H gave the allylic alcohol **20** in 80% isolated yield. The compound **20** was further converted into chiral epoxy alcohol **21** in 85% yield under Sharpless asymmetric epoxidation conditions[11] using (+)-DET, *t*-BuOOH and $Ti(O^iPr)_4$ (Scheme 3).



Scheme 3. Reagents and conditions: a) i) 2,2-DMP, *p*-TSA (cat), benzene, 0 °C - reflux, 78%; ii) LAH, THF, 0 °C – r.t, 90%; b) NaH, BnBr, THF, 0 °C – r.t, 80%; c) i) $(COCl)_2$, DMSO, Et_3N, DCM, -78 °C; ii) $Ph_3P{=}CHCO_2Et$, benzene, r.t, 6h, 90% (for 2 steps); d) $NiCl_2.6H_2O$, $NaBH_4$, MeOH, 0 °C – r.t, 82%; e) LAH, THF, 0 °C - rt, 85%; f) i) $(COCl)_2$, DMSO, Et_3N, DCM, -78 °C; ii) $Ph_3P{=}CHCO_2Et$, benzene, r.t, 6h, 90% (two steps); g) DIBAL-H, CH_2Cl_2, -20 °C – r.t, 2h, 80%; h) (+)-DET, $Ti(O^iPr)_4$, *t*-BuOOH, CH_2Cl_2, 4Å MS, -25 °C, 12h, 85%.

Further treatment of the epoxy alcohol **21** with 2,2-dimethoxypropane in the presence of CSA (camphorsulfonic acid) in dichloromethane gave the *anti*-tetrahydrofuran (THF) **22** as a sole product in one step in 86% yield through a regio- and stereoselective exo-cyclization.[16] Reductive removal of the benzyl ether using Pd-C/H_2 followed by mono tosylation[17] afforded the tosyl derivative **24**. Compound **24** was then exposed to NaH to give the terminal epoxide **25** in 75% yield with a retention of the chiral center. Regioselective opening of the epoxide **25** with Grignard reagent prepared freshly from 1-undecane bromide and magnesium gave the

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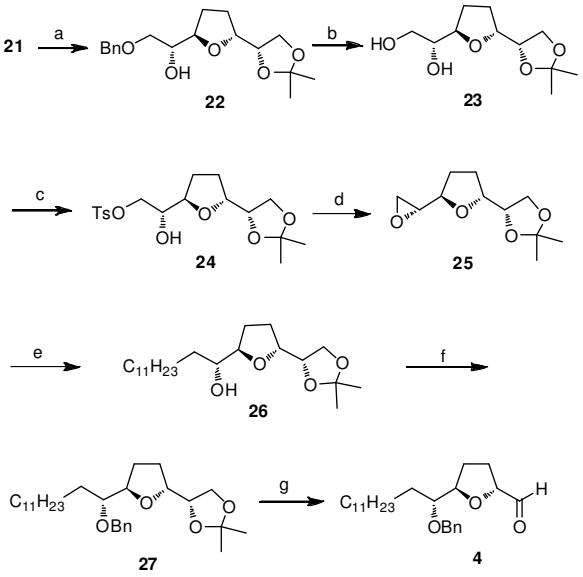
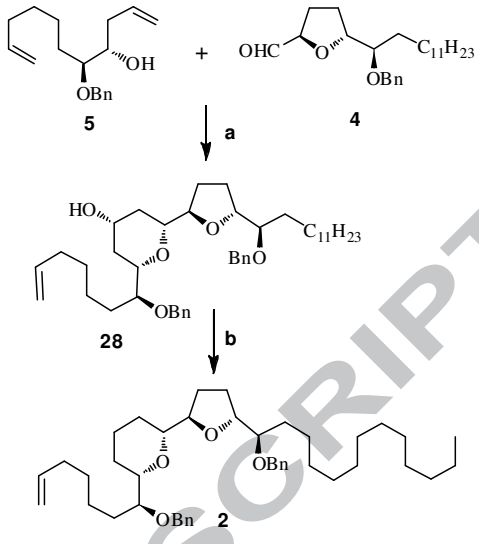
hydroxy derivative **26** in 86% yield. The secondary hydroxyl group of **26** was protected with benzyl bromide in presence of NaH in THF to yield the benzyl ether **27**. Removal of the isopropylidene group followed by oxidation of the diol using $NaIO_4$ furnished the aldehyde **4** in 75% overall yield (Scheme 4).



Scheme 4. Reagents and conditions: a) CSA, CH_2Cl_2, 0 °C, 5 min, 2,2-DMP, r.t, 2h, 86%; b) Pd/C(10%), H_2, EtOAc, r.t, 6h; c) Tosyl chloride, Et_3N, CH_2Cl_2, dibutyltinoxide, 2h, 75%; d) NaH, THF, 0 °C–r.t, 1h, 75%; e) *n*-$C_{11}H_{23}Br$, Mg, THF, -78 to 25 °C, 2h, 86%; f) NaH, BnBr, THF, 0 °C–r.t, 6h, 85%; g) i) *p*-TSA, MeOH, r.t, 2h; ii) $NaIO_4$, THF/H_2O (3:1), 75%.

Coupling of 4 and 5

The Prins cyclization has emerged as a powerful synthetic tool for the construction of tetrahydropyran scaffolds.[18] Inspired by the versatility of Prins cyclization, we attempted the coupling of homoallylic alcohol **5** with aldehyde **4** using trifluoroacetic acid in dichloromethane to produce the tetrahydropyranyl trifluoroacetate. No side reactions or byproducts were observed in Prins cyclization. But 15% unreacted aldehyde was recovered. Upon hydrolysis of the trifluoroacetate with K_2CO_3 in methanol furnished the desired tetrahydropyran-tetrahydrofuran (THP-THF) derivative **28** in 55% overall yield after two steps. The reaction is a highly diastereoselective and the required product **28** was obtained as a single diastereomer, which was confirmed by NMR spectrum of the crude product. The secondary hydroxyl group of **28** was converted into its xanthate ester[19] using NaH, CS_2 and MeI in dry THF, followed by deoxygenation (Barton-McCombie reaction)[20] using *n*-Bu_3SnH and a cat. amount of AIBN in toluene gave the target THP-THF core **2** in 80% yield (Scheme 5).[21]



Scheme 5. Reagents and conditions: a) i) TFA, CH_2Cl_2, 0 °C–r.t, 3h; ii) K_2CO_3, MeOH, 0 °C–r.t, 30 min, 55% (two steps); b) i) CS_2, MeI, NaH, THF, reflux, 6h, 85%; ii) *n*-Bu_3SnH, AIBN, toluene, reflux, 1h, 80%.

In conclusion, we have demonstrated a highly flexible and stereo-controlled synthetic route for the synthesis of tetrahydropyran-tetrahydrofuran (THP-THF) core **2** of (+)-muconin (**1**) employing Wittig olefination, Sharpless epoxidation, titanium(III) mediated reductive opening of 2,3-epoxy alcohol, regio- and stereoselective *exo*-cyclization of the epoxy alcohol, regio-controlled Grignard reaction, Prins-cyclization and Barton-McCombie reaction. Studies towards the total synthesis of (+)-muconin (**1**) through the coupling of fragments **2** and **3** is under progress.

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21 Spectral data for selected compounds. **((2*S*,3*S*)-3-(Hex-5-enyl)oxiran-2-yl)methanol (10)**: $[\alpha]_D^{20}$ + 6.24 (*c* = 0.83, $CHCl_3$); IR (neat): υ_{max} 3450, 2848, 1623, 770 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 5.83 - 5.69 (m, 1H), 5.02-4.89 (m, 2H), 3.90 - 3.81 (m, 1H), 3.64 - 3.53 (m, 1H), 2.94 - 2.83 (m, 2H), 2.30 (brs, 1H), 2.11 - 2.00 (m, 2H), 1.60 - 1.34 (m, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 138.5, 114.5, 63.2, 61.6, 58.5, 31.2, 28.4, 26.2, 25.2; ESI-MS: *m/z*: 179 (M+Na).
(*S*)-Nona-1,8-dien-3-ol (11): $[\alpha]_D^{20}$ −15.23 (*c* = 0.8, $CHCl_3$); IR (neat): υ_{max} 3420, 2915, 1640, 752 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 5.88 - 5.69 (m, 2H), 5.22 - 4.88 (m, 4H), 4.08 - 4.00 (m, 1H), 2.09 - 2.00 (m, 2H), 1.67 (bs, 1H), 1.55 - 1.25 (m, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 138.9, 137.8, 117.4, 114.1, 72.3, 37.0, 33.7, 29.1, 24.9; ESI-MS: *m/z*: 163 (M+Na).
(*S*)-2-((*S*)-1-(Benzyloxy)hept-6-enyl)oxirane (13): $[\alpha]_D^{20}$ + 6.56 (*c* = 1.26, $CHCl_3$); IR (neat): υ_{max} 3016, 2963, 1631, 1482, 724 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.34 - 7.25 (m, 5H), 5.82 - 5.68 (m, 1H), 5.01 - 4.89 (m, 2H), 4.53 (s, 2H), 3.23 - 3.16 (m, 1H), 2.86 - 2.82 (m, 1H), 2.74 - 2.69 (m, 1H), 2.67 - 2.63 (m, 1H), 2.09 - 1.99 (m, 2H), 1.64 - 1.36 (m, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 138.8, 138.6, 128.38, 128.3, 127.7, 114.4, 78.0, 72.2, 53.5, 43.1, 33.6, 32.7, 28.9, 24.6; ESI-MS: *m/z*: 247 (M+H), 269 (M+Na).
(4*S*,5*S*)-5-(Benzyloxy)undeca-1,10-dien-4-ol (5): $[\alpha]_D^{20}$ + 10.75 (*c* = 0.37, $CHCl_3$); IR (neat): υ_{max} 3430, 2920, 1624, 1460, 734 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.34 - 7.23 (m, 5H), 5.88 - 5.68 (m, 2H), 5.15 - 4.89 (m, 4H), 4.55 (dd, *J* = 11.3, 4.5 Hz, 2H), 3.78 - 3.72 (m, 1H), 3.37 - 3.31 (m, 1H), 2.28 - 2.20 (m, 2H), 2.08 - 1.99 (m, 2H), 1.66 – 1.28 (m, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 138.8, 138.4, 135.0, 128.4, 127.8, 127.6, 117.6, 114.3, 81.6, 72.1, 71.2, 36.8, 33.6, 29.0, 28.9, 25.0; ESI-MS: *m/z*: 297 (M+Na).
(*E*)-Ethyl 3-((4*R*,5*R*)-5-((benzyloxy)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)acrylate (16):

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$[\alpha]_D^{20}$ + 1.56 (*c* = 1.66, $CHCl_3$); IR (neat): υ_{max} 2930, 1725, 1648, 776 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.40 - 7.27 (m, 5H), 6.90 (dd, *J* = 15.6, 5.4 Hz, 1H), 6.09 (dd, *J* = 15.4, 1.1 Hz, 1H), 4.60 (s, 2H), 4.46 - 4.40 (m, 1H), 4.21 (q, *J* = 7.1 Hz, 2H), 4.01 - 3.93 (m, 1H), 3.63 (d, *J* = 4.7 Hz, 2H), 1.46 (s, 3H), 1.44 (s, 3H), 1.29 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 165.8, 143.9, 137.5, 128.2, 127.6, 127.5, 122.3, 110.0, 79.3, 77.2, 73.4, 69.1, 60.0, 26.7, 26.5, 14.0; ESI-MS: *m/z*: 321 (M+H), 343 (M+Na). **(*E*)-Ethyl-5-((4*R*,5*R*)-5-((benzyloxy)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)pent-2-enoate** (**19**): $[\alpha]_D^{20}$ + 12.83 (*c* = 2.26, $CHCl_3$); IR (neat): υ_{max} 2915, 1728, 1646, 768 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.38 -7.29 (m, 5H), 6.97 (dt, *J* = 15.6, 6.9 Hz, 1H), 5.83 (dt, *J* = 15.6, 1.5 Hz, 1H), 4.58 (s, 2H), 4.18 (q, *J* = 7.1 Hz, 2H), 3.88 - 3.78 (m, 2H), 3.62 - 3.48 (m, 2H), 2.47 - 2.23 (m, 2H), 1.80 - 1.60 (m, 2H), 1.41 (s, 3H), 1.39 (s, 3H), 1.29 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 166.1, 143.0, 138.4, 128.3, 127.7, 127.6, 121.8, 108.8, 79.6, 77.9, 73.5, 70.3, 59.9, 31.6, 28.6, 27.3, 27.0, 14.3; ESI-MS: *m/z*: 349 (M+H), 371 (M+Na).

((2*S*,3*S*)-3-(2-((4*R*,5*R*)-5-((Benzyloxy)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)ethyl) oxiran-2-yl)methanol (21): $[\alpha]_D^{20}$ + 1.67 (*c* = 0.6, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): δ 7.33 - 7.22 (m, 5H), 4.55 (s, 2H), 3.83 - 3.73 (m, 2H), 3.62 - 3.54 (m, 2H), 3.52 - 3.48 (m, 1H), 2.93 - 2.88 (m, 2H), 2.87 - 2.83 (m, 1H), 1.87 - 1.59 (m, 4H), 1.37 (s, 3H), 1,35 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 137.8, 128.4, 127.7, 127.6, 108.9, 79.8, 77.7, 73.5, 70.4, 61.6, 58.2, 55.3, 29.1, 27.8, 27.2, 26.9; ESI-MS: *m/z*: 322 (M) 345 $(M+Na)^+$

***(R)-2*-(Benzyloxy)-*1*-((2*R*,5*R*)-tetrahydro-5-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl) furan-2-yl)ethanol (22)**: $[\alpha]_D^{20}$ −5.63 (*c* = 0.8, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): δ 7.32 - 7.22 (m, 5H), 4.53 (s, 2H), 4.04 - 3.96 (m, 2H), 3.93 - 3.86 (m, 2H), 3.78 (dd, *J* = 8.0, 5.0 Hz, 1H), 3.61 (q, *J* = 5.0 Hz, 1H), 3.50 - 3.44 (m, 2H), 2.14 -2.07 (m, 1H), 2.00 - 1.94 (m, 1H), 1.93 - 1.89 (m, 1H), 1.87 - 1.75 (m, 1H), 1.37 (s, 3H), 1.31 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 137.8, 128.1, 127.5×2, 109.0, 79.9, 79.7, 77.6, 73.2, 72.4, 71.6, 67.1, 28.6, 27.6, 26.6, 25.1; ESI-MS: *m/z*: 322 (M), 345 (M+Na); HRMS ($C_{18}H_{26}O_5Na$): calcd 345.16725; found: 345.16599.

(*R*)-1-((2*R*,5*R*)-Tetrahydro-5-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)furan-2-yl) tridecan-1-ol (26) $[\alpha]_D^{20}$ + 3.42 (*c* = 0.6, $CHCl_3$); IR (Neat): υ_{max} 3450, 2922, 1472, 768 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 4.04 (dd, *J* = 8.3, 6.0 Hz, 1H), 3.94 - 3.70 (m, 4H), 3.31 (dd, *J* = 11.3, 6.0 Hz, 1H), 2.14 - 2.06 (m, 1H), 2.03 - 1.92 (m, 1H), 1.84 - 1.76 (m, 1H), 1.69 - 1.59 (m, 1H), 1.37 (s, 3H), 1.32 (s, 3H), 1.35 - 1.32 (m, 22H), 0.89 (t, *J* = 6.7 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 109.2, 82.9, 79.7, 77.8, 74.0, 67.2, 33.3, 31.9, 29.5×2, 29.2×2, 29.0, 28.6, 28.2, 28.0, 27.2, 26.5, 25.5, 25.2, 22.6, 14.0; ESI-MS: *m/z*: 393 (M+Na); HRMS ($C_{22}H_{42}O_4Na$): calcd 393.29753; found: 393.29627. **(*S*)-4-((2*R*,5*R*)-5-((*R*)-1-(Benzyloxy)tridecyl)-tetrahydrofuran-2-yl)-2,2-dimethyl-1,3-dioxolane** (**27**): $[\alpha]_D^{20}$ + 6.40 (*c* = 0.17, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ 7.33 - 7.18 (m, 5H), 4.61 (dd, *J* = 6.2, 11.7 Hz, 2H), 4.11 - 3.97 (m, 3H), 3.93 - 3.79 (m, 2H), 3.24 (dd, *J* = 10.5, 5.0 Hz, 1H), 2.12 - 2.04 (m, 1H), 1.99 - 1.88 (m, 1H), 1.80 - 1.58 (m, 2H), 1.37 (s, 3H), 1.32 (s, 3H), 1.46 - 1.19 (m, 22H), 0.88 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 139.0, 128.2, 127.8, 127.3, 109.2, 82.2, 81.5, 79.9, 78.2, 72.8, 67.6, 31.9, 30.9, 29.7, 29.6, 29.6×3, 29.3, 29.1, 28.3, 27.3, 26.7, 25.6, 25.3, 22.6, 14.1; ESI-MS: *m/z*: 461 (M+H), 478 $(M+NH_4)$; HRMS ($C_{29}H_{48}O_4Na$: calcd 483.34448; found: 483.34182.

(2*S*,4*S*,6*R*)-2-((*S*)-1-(Benzyloxy)hept-6-enyl)-6-((2*R*,5*R*)-5-((*R*)-1-(benzyloxy)tridecyl)-tetrahydrofuran-2-yl)-tetrahydro-2*H*-pyran-4-ol (**28**): $[\alpha]_D^{20}$ + 2.2 (*c* = 0.36, $CHCl_3$); IR (neat): υ_{max} 3434, 2926, 2851, 1628, 1463, 726 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.39 - 7.14 (m, 10H), 5.77 - 5.63 (m, 1H), 4.97 - 4.82 (m, 2H), 4.66 (t, *J* = 11.5 Hz, 2H), 4.52 (t, *J* = 12.4 Hz, 2H), 4.14 - 3.99 (m, 2H), 3.97 - 3.89 (m, 1H), 3.82 - 3.69 (m, 1H), 3.48 - 3.22 (m, 3H), 2.02 - 1.78 (m, 4H), 1.67 - 1.49 (m, 4H), 1.44 - 1.08 (m, 30H), 0.81 (t, *J* = 6.7 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 139.1, 138.88, 138.82, 132.1, 128.17, 128.12, 127.8, 127.4, 127.2, 114.2, 82.09, 82.0, 80.9, 80.7, 80.6, 77.5, 72.8, 72.6, 68.4, 36.8, 36.1, 34.5, 33.6, 33.5, 31.8, 30.7, 29.9, 29.7, 29.5, 29.2, 28.8, 28.3, 27.5, 27.4, 25.6, 25.18, 25.13, 22.6, 14.0; ESI-MS: *m/z*: 663 (M+H); HRMS ($C_{43}H_{66}O_5Na$): calcd 685.48025; found: 685.47833.

(2*S*,6*R*)-2-((*S*)-1-(Benzyloxy)hept-6-enyl)-6-((2*R*,5*R*)-5-((*R*)-1-(benzyloxy)tridecyl)-tetrahydrofuran-2-yl)-tetrahydro-2*H*-pyran (2): $[\alpha]_D^{20}$ + 18.0 (*c* = 0.1, $CHCl_3$); IR (neat): υ_{max} 2916, 2843, 1621, 1469, 739 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.31 - 7.14 (m, 10H), 5.74 - 5.66 (m, 1H), 4.92 - 4.82 (m, 2H), 4.67 (t, *J* = 11.6 Hz, 2H), 4.52 (dd, *J* = 19.8, 11.6 Hz, 2H), 4.06 - 4.00 (m, 1H), 3.91 - 3.86 (m, 1H), 3.44 - 3.39 (m, 1H), 3.35 - 3.30 (m, 1H), 3.29 - 3.27 (m, 2H), 1.97 - 1.69 (m, 4H), 1.62 - 1.32 (m, 16H), 1.30 - 1.05 (m, 20H), 0.81 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 139.28, 139.2, 139.0, 128.18, 128.13, 127.9, 127.8, 127.3, 127.2, 114.1, 81.9, 81.4, 81.2, 80.1, 79.9, 72.9, 72.6, 68.8, 34.0, 33.7, 31.9, 30.7, 30.0, 29.7, 29.6, 29.4, 29.2, 29.1, 28.9, 28.3, 27.5, 27.3,28.0, 27.2, 26.4, 25.7, 25.3, 22.7, 14.1; ESI-MS: *m/z*: 664 $(M+NH_4)^+$.

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