

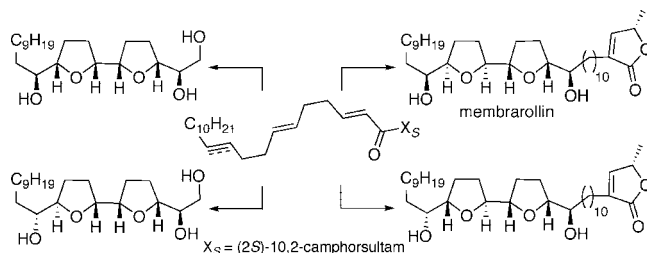
Oxidative Cyclization Reactions of Trienes and Dienynes: Total Synthesis of Membrarollin

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Trienes and dienynes containing one electron-deficient double bond were shown to undergo regio- and stereoselective oxidative cyclization in the presence of permanganate ion to afford 2,5-bis-hydroxyalkyltetrahydrofurans (THF diols). The THF diols produced retained either alkene or alkyne functionalities, which provided convenient handles for the metal oxo-mediated introduction of an adjacent THF ring with overall control of relative and absolute stereochemistry. Adjacent bis-THFs possessing *threo-cis-threo-trans-erythro*, *threo-cis-threo-trans-threo*, *threo-cis-threo-cis-erythro*, *threo-cis-erythro-cis-threo*, or *threo-cis-erythro-trans-threo* relationships were synthesized by appropriate selection of alkene geometry and methodology for the closure of the second ring. The *threo-cis-threo-cis-erythro* stereochemical arrangement is embodied within the bis-THF core units of a number of *Annonaceous* acetogenins including membrarollin, while trilobacin has a *threo-cis-erythro-trans-threo* configured core. As an application of the selective oxidative cyclization approach, a total synthesis of membrarollin was completed in 17 linear steps from dodecyne. The C21,C22 double epimer of membrarollin was also synthesized in 15 linear steps and without recourse to the use of hydroxyl group protection.

Introduction

The class of compounds known as *Annonaceous* acetogenins has stimulated substantial interest from synthetic chemists due to the identification of diverse and important biological activities, not least of which is the potent cytotoxic antitumor activity

exhibited by many family members.¹ The *Annonaceous* acetogenins have also been a focus of synthetic effort because their structures provide a platform to inspire and advance methodology.^{2,3} Structurally, most *Annonaceous* acetogenins can be grouped into four subclasses: mono-THFs, adjacent bis-THFs, nonadjacent bis-THFs, and nonclassical acetogenins containing a 2,6-disubstituted tetrahydropyran (THP) ring. Acetogenins containing epoxide rings or unsaturation within their C1–C32/34 backbone are also known, and these compounds have been proposed as biosynthetic precursors to THF- and THP-contain-

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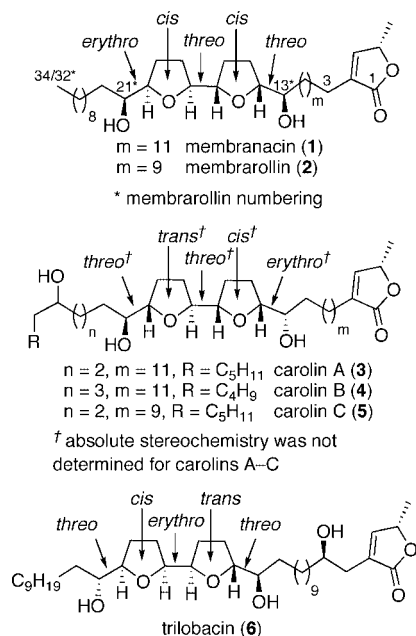


FIGURE 1. Structures of representative adjacent bis-THF acetogenins containing *cis*-THF rings.

ing acetogenins. Within the adjacent bis-THF category, over 20 members are known that contain at least one *cis*-2,5-disubstituted THF ring (Figure 1).^{1a,4} Assignment of relative and absolute stereochemistry in the bis-hydroxyalkyl tetrahydrofuran (THF diol) regions present in acetogenins has been complicated because these waxy compounds are not typically amenable to structural determination by X-ray diffraction. Therefore, stereochemical assignment has relied heavily on empirical rules relating to NMR chemical shift data, which have

developed through careful analysis of NMR spectra of synthetic model compounds, the natural products themselves, and various derivatives such as Mosher esters.^{1,4c,5–7}

The antitumor activity of acetogenins has been attributed to their inhibitory effect on mitochondrial NADH-ubiquinone oxidoreductase (complex I) and to inhibition of ubiquinone-linked NADH oxidase present in membranes of cancerous cells.⁸ Adjacent bis-THF acetogenins including membrarollin (2, IC₅₀ 0.3 nM) and membranacin (1, IC₅₀ 0.6 nM) rank among the most potent of the known inhibitors of complex I.⁹ The stereocontrolled assembly of the adjacent bis-THF diol units represents the most significant challenge to be addressed during total syntheses of this subclass of acetogenins, and various strategies have been investigated.^{2,3,10} Oxidative cyclization of 1,5-dienes constitutes a powerful method that enables the stereoselective formation of 2,5-disubstituted THF diols containing up to four new stereogenic centers in a single step.^{11–13} Any of eight possible stereoisomeric *cis*-2,5-disubstituted THF diols may be obtained through control of diene stereochemistry and diastereofacial selectivity of the initial reaction between the oxidant and the substrate. While different metal oxo species may induce the oxidative cyclization of 1,5-dienes to *cis*-2,5-disubstituted THF diols, permanganate ion remains the only one

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that affords direct access to enantiomerically enriched products in a single step, either through the use of chiral auxiliaries or asymmetric phase-transfer catalysis.¹⁴ In principle, the insoluble coproduct of permanganate oxidations, MnO_2 , could be recycled by sequential air and electrochemical oxidations.¹⁵ However, the very low cost of KMnO_4 coupled with the relatively low toxicities of MnO_2 or Mn(II) salts renders recycling unnecessary for typical laboratory-scale experiments.

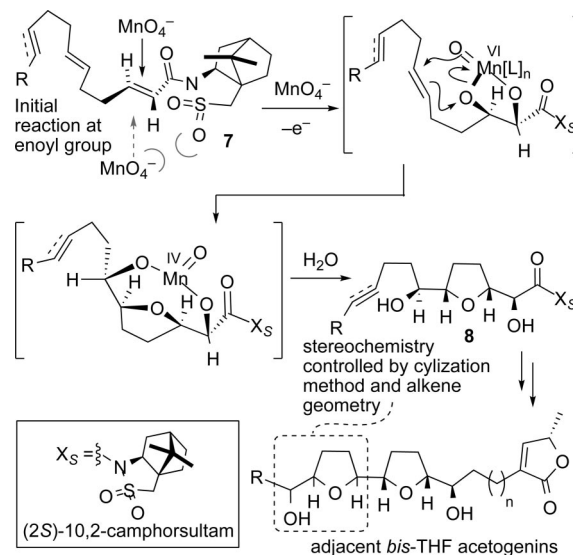
In this paper we present our studies on the reactions of dienynes and trienes with permanganate ion and show that selective oxidative cyclizations are possible. Furthermore, the THF diols produced in these selective oxidative cyclizations may serve as convenient precursors to adjacent bis-THFs. We go on to illustrate the synthetic value of the methodology through the total synthesis of the *Annonaceous* acetogenin membrarollin,¹⁶ and we also show how the bis-THF core unit present in other acetogenins can be accessed by this approach.

Results and Discussion

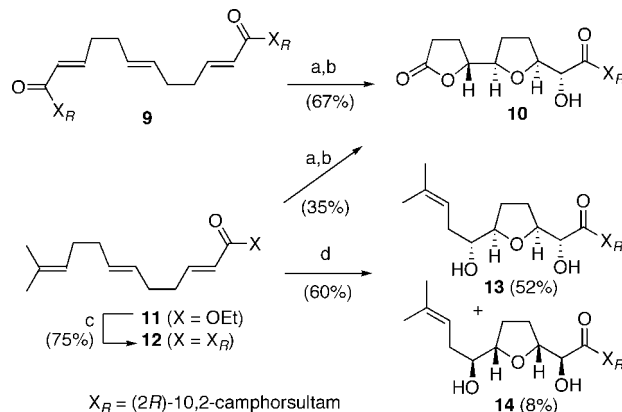
Whereas selective osmylations of dienes, trienes, and enynes have been well-studied,^{17,18} the corresponding reactions of permanganate ion remain relatively unexplored. In contrast to other metal oxo species, permanganate oxidizes alkenes more rapidly when electron-withdrawing substituents such as carbonyl groups are conjugated with the olefin.¹⁹ Furthermore, alkynes react more slowly with permanganate than alkenes.²⁰ These observations suggest that selective oxidative cyclizations of suitable dienynes and trienes should be possible. Thus, regio- and stereoselective oxidative monocyclizations of 1,5,9-trienes or related dienynes (e.g., **7**) could be used advantageously, to yield THF diols containing unsaturated functionality suitable for elaboration using metal oxo or metal peroxo species to give bis-THFs (Scheme 1). An advantage of this two-stage cyclization approach would lie in the ability to control the stereochemistry within the second ring system, depending on the cyclization methodology employed.

Previously, we demonstrated that oxidation of trienes such as **9**, in the presence of excess KMnO_4 , gave bifuranyl systems **10** in good yield (Scheme 2),^{12c,21} while oxidation of an unsymmetrical triene **12** under similar conditions was less efficient. These results provided an indication that trienoic acid derivatives could undergo selective oxidative cyclization initi-

SCHEME 1. Synthetic Route to Adjacent Bis-THF Acetogenins by Selective Oxidative Cyclization of Dienynoyl or Trienoyl Sultams



SCHEME 2. Oxidative Cyclizations of Trienoyl Sultams^a



^a Reagents and conditions: (a) KMnO_4 (2.6 equiv), adogen 464 (5–10 mol %), acetone/AcOH (3:2), $-25\text{ }^\circ\text{C}$; (b) $\text{NaIO}_4\text{-SiO}_2$, CH_2Cl_2 , $0\text{ }^\circ\text{C}$; (c) (i) NaOH , NaHCO_3 , $\text{MeOH-H}_2\text{O}$, $80\text{ }^\circ\text{C}$, (ii) $\text{C}_6\text{F}_5\text{OH}$, DCC, EtOAc, (iii) (2*R*)-10,2-camphorsultam, *n*-BuLi, THF, $-78\text{ }^\circ\text{C}$ to rt; (d) KMnO_4 (1.8 equiv), adogen 464 (5 mol %), acetone/AcOH (3:2), $-25\text{ }^\circ\text{C}$.

ated at the α,β -unsaturated alkene and that a more slowly oxidized alkene might be retained in the product. Indeed, this expectation was realized when oxidative cyclization of **12** using fewer equivalents of permanganate delivered a separable mixture of diastereoisomeric THF diols **13** and **14** (dr = 6:1) with the trisubstituted alkene still intact.

This enhanced knowledge of the regioselective oxidative cyclization of trienoates presented a vantage point from which we could design novel routes to adjacent bis-THFs and apply this methodology to the synthesis of acetogenins such as membrarollin (**2**) (Scheme 1). The successful selective oxidative monocyclization of triene **12** suggested that two sequential oxidative cyclization reactions of a suitably substituted triene or a dienyne, already carrying the left-hand chain present in the natural product, could establish the adjacent bis-THF subunit with stereocontrol and in short order. Toward this end dienynes **15a,b** and trienoic acid derivative **26** were synthesized (Schemes 3 and 5). The dienyne substrate **15a** was chosen as a surrogate for **26** as the remaining triple bond has the potential to serve as

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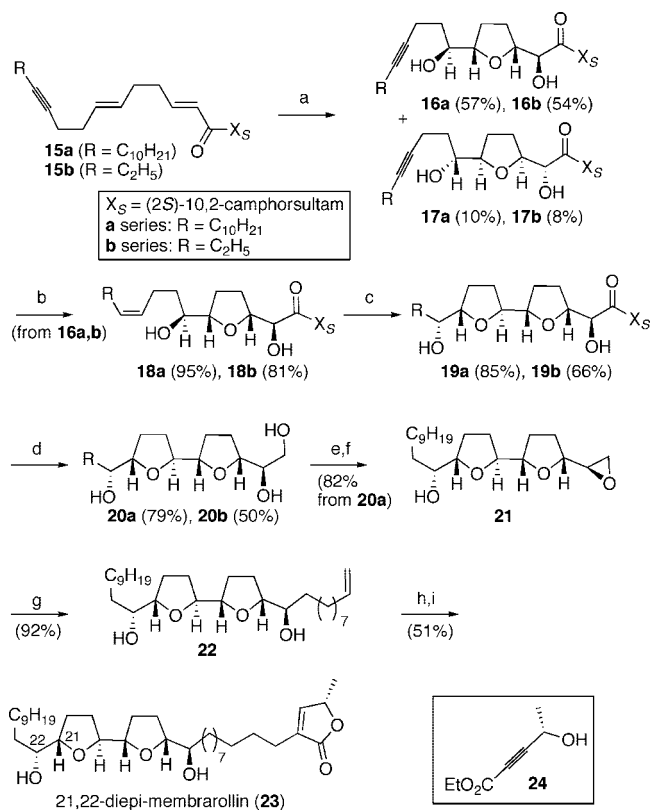
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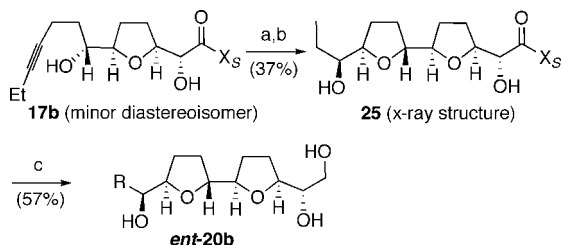
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SCHEME 3. Metal Oxo-Mediated Synthesis of Adjacent Bis-THFs^a

^a Reagents and conditions: (a) KMnO₄, acetone/AcOH; (b) H₂, Pd/BaSO₄ or Pd/CaCO₃, quinoline; (c) Re₂O₇, THF, TFAA; (d) NaBH₄, THF, H₂O; (e) Bu₂SnO, PhH, then TsCl, TBAB; (f) DBU, CH₂Cl₂; (g) CH₂=CH-(CH₂)₇MgBr, CuI, THF; (h) **24**, CpRu(COD)Cl, CH₃OH; (i) TsNHNH₂, THF, NaOAc, H₂O.

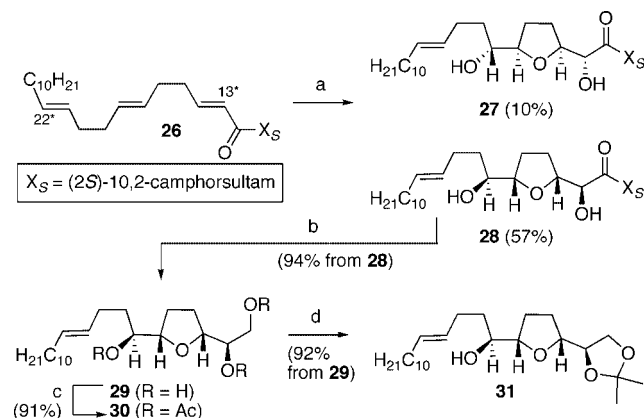
SCHEME 4. Stereochemical Determination for the Bis-THFs^a

^a Reagents and conditions: (a) H₂, Pd/BaSO₄ or Pd/CaCO₃, quinoline; (b) Re₂O₇, THF, TFAA; (c) NaBH₄, THF, H₂O.

a precursor to either olefin stereoisomer,²² while a shorter chain analogue **15b** was prepared with the expectation that it would later yield crystalline derivatives to assist structural assignment.

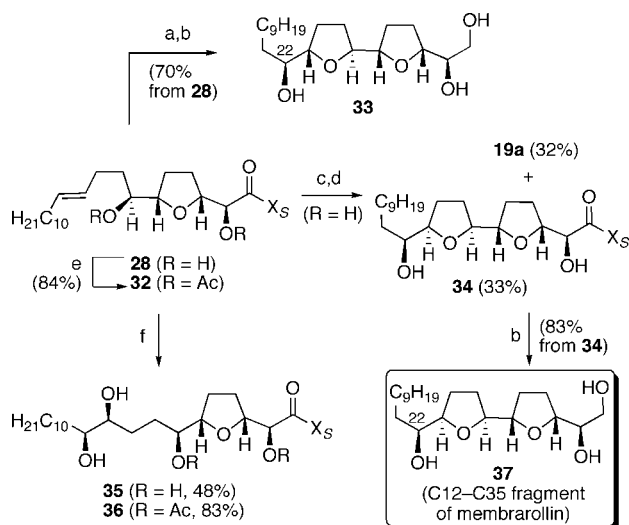
Permanganate-mediated cyclization of dienes **15a/b** afforded the readily separable diastereomeric THF diols **16a/b** and **17a/b** (dr **16/17** = 6:1 from ¹H NMR) in 62–67% combined yields (Scheme 3). Semihydrogenation of the triple bond in **16a** gave the bis-homoallylic alcohol **18a**, which underwent a second efficient metal oxo-mediated cyclization to afford a single bis-THF **19a**.^{13c,23} The absolute configuration of the newly created C22 stereogenic center was established through NMR experiments carried out on mono- and bis-Mosher ester derivatives

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SCHEME 5. Selective Oxidative Cyclization of Triene **26**^a

^a Membrarollin numbering

^a Reagents and conditions: (a) KMnO₄ (1.3 equiv), acetone/AcOH (4:1); (b) NaBH₄ (1.1 equiv), THF, H₂O (0.1%); (c) Ac₂O, pyr, 95 °C; (d) (MeO)₂CMe₂, TsOH.

SCHEME 6. Transformations of the Hydroxyolefin Intermediates^a

^a Reagents and conditions: (a) Re₂O₇, THF, TFAA; (b) NaBH₄ (1.1 equiv), THF, H₂O (0.1%); (c) *m*-CPBA, CH₂Cl₂; (d) CSA, CH₂Cl₂; (e) Ac₂O, pyr, Δ; (f) AD-mix α, MeSO₂NH₂, *t*-BuOH–H₂O.

of epoxide **21** and diol **22**, respectively.⁵ The stereochemical assignment of the bis-THF **19a** was later corroborated by carrying out the same sequence of reactions on THF-diols **16b** and **17b** (R = Et) to give bis-THFs **19b** and **25**, respectively (Schemes 3 and 4). The bis-THF **25** proved to be suitable for X-ray structural determination.²⁴ Reduction of **25** and **19b** using NaBH₄ led to the formation of triols **20b** and *ent*-**20b** that were shown to be enantiomeric, thereby confirming the structure of **19b** and supporting the stereochemical assignment of **19a**.

(23) For examples of directed oxidative cyclization of 5-hydroxyolefins using rhenium oxo species, see refs 3a, l, n, p, u and (a) D'Souza, L. J.; Sinha, S. C.; Lu, S. F.; Keinan, E.; Sinha, S. C. *Tetrahedron* **2001**, *57*, 5255–5262. (b) Morimoto, Y.; Iwai, T.; Kinoshita, T. *J. Am. Chem. Soc.* **1999**, *121*, 6792–6797. (c) Morimoto, Y.; Iwai, T. *J. Am. Chem. Soc.* **1998**, *120*, 1633–1634. (d) Sinha, S. C.; Keinan, E.; Sinha, S. C. *J. Am. Chem. Soc.* **1998**, *120*, 9076–9077. (e) Towne, T. B.; McDonald, F. E. *J. Am. Chem. Soc.* **1997**, *119*, 6022–6028. (f) Sinha, S. C.; Sinha-Bagchi, A.; Keinan, E. *J. Am. Chem. Soc.* **1995**, *117*, 1447–1448. (g) Tang, S. H.; Kennedy, R. M. *Tetrahedron Lett.* **1992**, *33*, 5299–5302.

(24) Light, M. E.; Morris, C. L.; Brown, R. C. D. (2008) Personal communication to the Cambridge Structural Database, deposition number CCDC 686179.

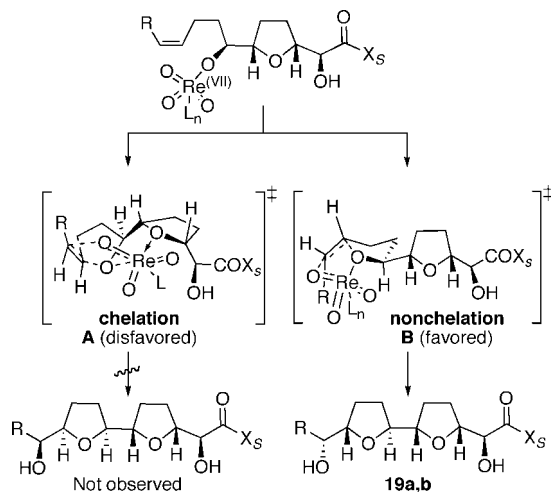


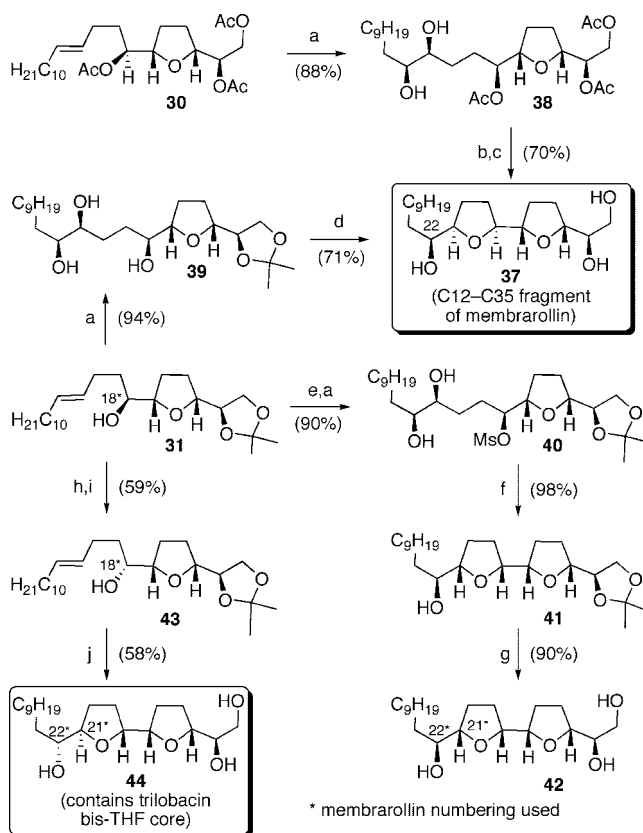
FIGURE 2. Transition state models for the perrhenate-mediated cyclization of compounds **18a,b**.

The bis-THF derivative **19a** was further elaborated by reduction of the acylsultam to the diol **20a**, formation of epoxide **21**, and cuprate addition to afford alkene **22** (Scheme 3). The synthesis of the C21,C22 bis-epimer **23** of membrarollin was completed using the Trost ruthenium-catalyzed Alder-ene reaction to introduce the butenolide,^{3r,25} followed by diimide reduction of the C4–C5 alkene. Notably, this metal oxo-mediated approach avoided the requirement for hydroxyl protection during the synthesis of a complex acetogenin stereoisomer.

The stereochemical outcome of the second metal oxo-mediated cyclization reaction requires some comment because *cis* and *trans* selectivities have been reported for related systems and rationalized by invoking either steric or chelation control models.^{31,23} The chelation control model **A** can be compared to those proposed for the reactions of manganese(VI) and osmium(VI) diester intermediates during oxidative cyclizations of 1,5-dienes and dihydroxyalkenes, respectively (see Scheme 1 for cyclization of Mn(VI) intermediate), where the geometrical constraints imposed by chelation confer “*cis*” selectivity to the ensuing oxidative cyclization (Figure 2).¹¹ Therefore, when an effective coordinating substituent is present in the substrate adjacent to the hydroxyl group, chelation control may be observed in rhenium oxo-mediated cyclizations.^{3a,23c,d} However, the perrhenate-mediated oxidation of our substrates **18a,b** yielded the *trans*-configured products **19a,b**, indicating that the nonchelation model is in operation despite the presence of THF oxygens vicinal to the reacting hydroxyl groups (transition state model **B**, Figure 2).²⁶ In this case, chelation control (model **A**) may be disfavored by adverse steric interactions between the metal oxo complex and the hydroxyacylsultam group across the original *cis*-THF ring.

Attention then turned to the selective oxidation of the triene system **26**, revealing that permanganate-mediated oxidative cyclization also proceeds with high regioselectivity, affording the two separable diastereomeric THF diols **27** and **28** (Scheme 5). The presence of the C21–C22 alkene (membrarollin numbering) did not affect the efficiency of the cyclization significantly, and no major byproducts arising from oxidation at this site were identified. In order to develop stereodivergent

SCHEME 7. Synthesis of Stereoisomeric Bis-THF Core Units^a



^a Reagents and conditions: (a) AD-mix α , MeSO₂NH₂, *t*-BuOH–H₂O; (b) SOCl₂, pyr, CH₂Cl₂, then RuCl₃·H₂O, NaIO₄, MeCN–H₂O; (c) K₂CO₃, MeOH, then 2 M H₂SO₄; (d) MeC(OMe)₃, BF₃·OEt₂, CH₂Cl₂, 0 °C, then K₂CO₃, MeOH; (e) MsCl, Et₃N, CH₂Cl₂; (f) pyr, Δ ; (g) HCl, dioxane; (h) *p*-NO₂C₆H₄CO₂H, PPh₃, DIAD, THF; (i) NaOH, MeOH; (j) Re₂O₇, THF, TFAA.

approaches to introduce the second THF ring, several different oxidative methods were investigated, including epoxidation-cyclization, dihydroxylation-cyclization, and direct metal oxo-mediated cyclization (Schemes 6 and 7). Direct perrhenate-mediated cyclization of THF diol **28** was found to lead selectively to the *threo-cis-threo-trans-threo* configured bis-THF triol **33** after reductive cleavage of the sultam auxiliary.²⁷ Alternatively, epoxidation of **28** in the presence of *m*-CPBA followed by exposure to CSA gave a separable mixture of bis-THFs **19a** and **34** with no selectivity (**19a** was previously obtained selectively from perrhenate cyclization of the (*Z*)-hydroxyolefin **18a**; see Scheme 3).²⁸ The bis-THF **34** contains the correct relative and absolute stereochemistry required for membrarollin, but attempts to develop a diastereoselective synthesis of **34** using the Shi epoxidation catalyst were not successful.²⁹ Therefore attention shifted to a dihydroxylation–

(25) In addition to the desired butenolide, a minor regioisomeric Alder-ene product was isolated (see Supporting Information).

(26) For other examples of *trans*-selective cyclizations see refs 3n and 23b.

(27) The stereochemical assignment of **33** was supported by conversion to an epoxyalcohol derivative, (*S*)-1-((2*S*,5*S*)-5-((2*S*,5*R*)-5-((*R*)-oxiran-2-yl)-tetrahydrofuran-2-yl)-tetrahydrofuran-2-yl)undecan-1-ol, and analysis of the NMR data of its C22 Mosher ester derivatives (see Supporting Information). On this basis the configuration at C22 (membrarollin numbering) was determined to be *S*. The *threo* relationship between the C22 hydroxyl group and the C21 THF oxygen is evident from the chemical shift of the C22 methine proton in (*S*)-1-((2*S*,5*S*)-5-((2*S*,5*R*)-5-((*R*)-oxiran-2-yl)-tetrahydrofuran-2-yl)-tetrahydrofuran-2-yl)undecan-1-ol (δ 3.39 ppm; see ref 6c) and is of course expected as a result of the stereospecific nature of the oxidative cyclization.

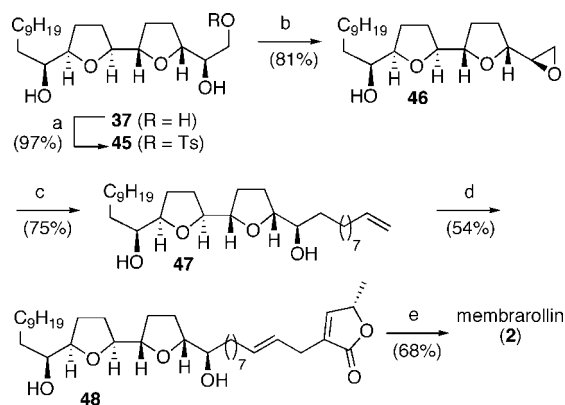
(28) Gu, Z. M.; Fang, X. P.; Zeng, L.; Song, R.; Ng, J. H.; Wood, K. V.; Smith, D. L.; McLaughlin, J. L. *J. Org. Chem.* **1994**, *59*, 3472–3479.

cyclization sequence. Sharpless asymmetric dihydroxylation (AD) of **28** yielded a single tetraol **35** in a modest 48% yield,³⁰ and although no other products were evident in the reaction mixture, we were not able to improve upon this result. However, we discovered that dihydroxylation of the less polar derivative **32** gave the diol **36** in an improved 83% yield (Scheme 6). Consequently, triacetate- and acetonide-protected triol derivatives **30** and **31** were synthesized for application in further dihydroxylation–cyclization studies (Scheme 5).

Sharpless AD reactions of the alkenes **30** and **31** returned the corresponding diol **38** and triol **39** in high yields (Scheme 7). Cyclization of the diol **38** could be carried out by way of a cyclic sulfate intermediate, which upon exposure to methoxide gave bis-THF **37** as its C22 monosulfate ester.³¹ Under acidic workup conditions the sulfate ester was hydrolyzed to provide the triol **37**, with the correct configuration needed for a total synthesis of membrarollin. Alternatively, cyclization could be effected through formation of an intermediate oxocarbenium species by reaction of triol **39** with trimethyl orthoacetate in the presence of $\text{BF}_3 \cdot \text{OEt}_2$ (step d, Scheme 7).³² Under these conditions, the oxocarbenium ion underwent ring opening by the pendant C18 hydroxyl group with inversion at C21, also delivering the *threo-cis-threo-cis-erythro* configured bis-THF diol system, protected as its C22 monoacetate. The acetonide protection was cleaved during the cyclization, and partial acetylation of the primary hydroxyl group was observed. The fact that the stereochemical integrity at C13 was not disturbed during the acylation was confirmed by treatment of the mixture or the isolated diacetate with $\text{MeOH}/\text{K}_2\text{CO}_3$, to give an improved yield of the same triol **37** obtained from the cyclic sulfate route.

The *threo-cis-erythro-trans-threo* bis-THF core present in another group of bis-THF acetogenins, exemplified by trilobacin (**5**),³³ can also be accessed from hydroxyolefin **31** by inversion of the C18 alcohol and subsequent perhenate-mediated cyclization (Scheme 7). Inversion of the secondary alcohol **31** was achieved through a Mitsunobu hydrolysis sequence to afford its *threo-cis-erythro* epimer **43**.³ⁿ Hydroxyolefin **43** underwent rhenium-promoted cyclization, with cleavage of the acetonide protection, to give a single diastereoisomeric triol **44** containing the trilobacin bis-THF core stereochemistry. A complementary

SCHEME 8. Total Synthesis of Membrarollin^a



^a Reagents and conditions: (a) Bu_2SnO , PhH , then TsCl , TBAB ; (b) K_2CO_3 , MeOH ; (c) $\text{H}_2\text{C}=\text{CH}(\text{CH}_2)_7\text{MgBr}$ bromide, CuBr , THF , -60 to -30 °C; (d) **24**, $\text{CpRu}(\text{MeCN})_3^+\text{PF}_6^-$, DMF , rt ; (e) TsNHNH_2 , THF , NaOAc , H_2O .

approach, involving mesylation of **31** followed by asymmetric dihydroxylation and cyclization returned *cis-cis* bis-THF **41** in high overall yield. Cleavage of the acetonide group from **41** afforded the diastereoisomeric triol **42**, which served to assist in the structural assignment of **44**.³⁴

With two efficient routes to the bis-THF triol **37** secured, the total synthesis of membrarollin was readily achieved through application of a five-step sequence similar to that described above for the bis-epimer **23** (Scheme 8). Synthetic membrarollin prepared in our laboratory gave ^1H and ^{13}C NMR data that were in excellent agreement with those reported for the isolated natural product.^{35,36}

Summary

In conclusion, we have demonstrated that dienyne and trienes containing one electron-poor double bond can undergo selective oxidative cyclization in a reliable and predictable fashion when limiting permanganate is employed. The fact that these oxidative cyclization reactions are initiated at the enoyl group provides a means to control the stereochemistry within the THF diol unit using chiral auxiliaries. In this way enantiomerically enriched THF diols containing unsaturated side chains can be accessed and subsequently manipulated through oxidative processes to afford bis-THF diol stereoisomers. Thus, a synthesis of membrarollin was completed in nine linear steps from trienoyl sultam **26** by application of this general strategy, and an approach to the *threo-cis-erythro-trans-threo* configured core found in trilobacin was also realized. Additionally, bis-THF diols pos-

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(33) For total synthesis of trilobacin see ref 3u. For formal synthesis, see: Dabideen, D.; Ruan, Z. M.; Mootoo, D. R. *Tetrahedron* **2002**, *58*, 2077–2084.

(34) The expected C21,C22 (membrarollin numbering) *threo* relationship in structures **41**, **42**, and **44** was supported by the resonance of the C22 methine protons in the range 3.3–3.5 ppm, whilst the C17,C18 *erythro* relationship in **43** was indicated by a downfield shift for the C18 methine proton (in the range 3.7–3.9 ppm) compared to **31** (in the range 3.3–3.5 ppm).^{6c} The configurations of **42** and **44** can therefore be assigned on the basis of the predictable stereochemical outcome for the sequence of reactions **31** → **44**, and the precedent for *trans* selectivity in the rhenium cyclization (e.g. **18a,b** → **20a,b** and **28** → **33**).

(35) In principle, there are eight stereoisomers of membrarollin that would be likely to exhibit substantially identical NMR spectra,^{7a} which can be reduced to four possibilities if the stereochemistry of the butenolide is assumed to be 3*4S* as is the case other known acetogenins. Structures with pseudo enantiomeric bis-THF core units (1*3R*,1*4R*,1*7S*,1*8S*,2*1R*,2*2S* and 1*3S*,1*4S*,1*7R*,1*8R*,2*1S*,2*2R*) and structures where the C14 and C23 chains were switched (2*2R*,2*1R*,1*8S*,1*7S*,1*4R*,1*3S* and 2*2S*,2*1S*,1*8R*,1*7R*,1*4S*,1*3R*) would be possible candidates for the isolated natural product. During the isolation work, connectivity and stereochemical assignment of membrarollin was carried out by first synthesizing C13 and C22 mono-urethane derivatives from the natural product.^{4c} Using these derivatives, the absolute stereochemistry of the C22 and C13 carbinol centers were determined using the Mosher ester method leading to the conclusion that membrarollin was the 1*3R*,1*4R*,1*7S*,1*8S*,2*1R*,2*2S* isomer.

(36) The optical rotation value obtained from our synthetic sample of membrarollin differed from that reported.^{4c} Our sample: $[\alpha]_D^{27} +23.5$ (c 0.95, CHCl_3) and $+27.1$ (c 0.51, MeOH); lit.^{4c} $+10$ (c 0.8, MeOH); mp 43–45 °C (no reported mp). However, reported^{4a,b} rotation values for membranacin (**1**) are very similar to our value for **2**, which would be expected on the basis of the structural similarity between **1** and **2**.

sessing *threo-cis-threo-trans-threo*, *threo-cis-threo-trans-erythro*, and *threo-cis-erythro-cis-threo* configurations can be accessed from trienes or dienynes, and application of the dual Mn/Re metal oxo-mediated route circumvented the requirement for hydroxyl group protection during a short synthesis of 21,22-di-epi-membrarollin (**23**).

Experimental Section

(2S)-N-((2S)-2-Hydroxy-2-((2R,5S)-5-((1S,4E)-1-hydroxypentadec-4-enyl)-tetrahydrofuran-2-yl)ethanoyl)-camphor-10,2-sultam (28). To a solution of triene **26** (980 mg, 1.89 mmol) in acetone (64 mL) and AcOH (16 mL) at 30 °C was added KMnO₄ (389 mg, 2.46 mmol). The solution immediately turned purple and then to brown over ~5 min. The mixture was stirred between -30 and -20 °C for 2 h before quenching with saturated aqueous Na₂S₂O₅ (8 mL) and H₂O (8 mL). The aqueous phase was extracted with EtOAc (4 × 15 mL), and the combined organic phases were dried (Na₂SO₄) and concentrated in vacuo to a yellow oil. Purification by column chromatography (silica gel, 20% → 40% EtOAc/hexane) afforded three different fractions. The major diastereoisomer **28** (611 mg, 1.08 mmol, 57%) was obtained as a thick colorless gum, the minor diastereoisomer **27** (103 mg, 0.18 mmol, 10%) as a cream solid, and (2S)-N-((2R,5E,10E)-2-hydroxy-3-oxohenicosa-6,10-dienyl)-camphor-10,2-sultam (124 mg, 0.23 mmol, 12%) as a yellow oil. **Data for 28:** [α]_D²⁶ +27.6 (c 0.75, CHCl₃); IR $\nu_{\max}$ (neat) 3458, 2956, 2923, 2853, 1696 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 5.50–5.36 (2H, m), 4.62–4.52 (2H, m), 3.97 (1H, dd, *J* = 7.8, 4.9 Hz), 3.96–3.91 (1H, m), 3.88 (1H, dt, *J* = 7.3, 4.2 Hz), 3.52 (1H, d, *J* = 13.7 Hz), 3.51–3.44 (2H, m), 3.45 (1H, d, *J* = 13.7 Hz), 2.30–2.15 (1H, m), 2.15–2.01 (8H, m), 2.01–1.82 (6H, m), 1.66–1.41 (2H, m), 1.40–1.22 (16H, m), 1.17 (3H, s), 0.98 (3H, s), 0.89 (3H, t, *J* = 6.9 Hz) ppm; ¹³C NMR (100 MHz, CDCl₃) δ 171.7, 131.2, 129.5, 83.0, 78.7, 73.6, 73.4, 65.8, 53.1, 49.0, 47.9, 44.6, 38.2, 34.5, 32.9, 32.6, 31.9, 29.6, 29.6, 29.5, 29.3, 29.2, 28.8, 28.2, 26.4, 22.7, 20.8, 19.9, 14.1 ppm; LRMS (ES⁺) *m/z* 590 ([M + Na]⁺); HRMS (ES⁺) for C₃₁H₅₃NO₆Na⁺, calcd 590.3486, found 590.3503. **Data for 27:** [α]_D²⁶ +84.7 (c 1.20, CHCl₃); IR $\nu_{\max}$ (neat) 3482, 2956, 2922, 2853, 1693 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 5.49–5.35 (2H, m), 4.68 (1H, d, *J* = 2.3 Hz), 4.50 (1H, ddd, *J* = 7.4, 4.9, 2.3 Hz), 3.96 (1H, app t, *J* = 6.1 Hz), 3.77 (1H, td, *J* = 7.3, 4.5 Hz), 3.54–3.42 (1H, m), 3.50 (1H, d, *J* = 13.7 Hz), 3.45 (1H, d, *J* = 13.7 Hz), 2.24–1.84 (13H, m), 1.57–1.43 (2H, m), 1.42–1.20 (18H, m), 1.16 (3H, s), 0.98 (3H, s), 0.89 (3H, t, *J* = 6.9 Hz) ppm; ¹³C NMR (100 MHz, CDCl₃) δ 173.1, 131.1, 129.5, 83.0, 80.2, 74.2, 73.0, 64.9, 53.0, 49.0, 47.9, 44.5, 37.6, 34.5, 32.6, 31.9, 29.6, 29.5, 29.3, 29.2, 28.7, 28.2, 27.8, 26.5, 22.7, 20.4, 19.9, 14.1 ppm; LRMS (ES⁺) *m/z* 590 ([M + Na]⁺).

(1R)-1-((2R,5S)-5-((1S,4E)-1-Hydroxypentadec-4-enyl)-tetrahydrofuran-2-yl)-ethane-1,2-diol (29). To a solution of mono-THF **28** (1.00 g, 1.76 mmol) in THF (25 mL) and H₂O (25 mL) was added NaBH₄ (0.07 g, 1.94 mmol). The resulting mixture was stirred for 3 h, then H₂O (10 mL) was added, and the mixture was extracted with EtOAc (3 × 100 mL). The combined organic phases were dried (Na₂SO₄) and concentrated in vacuo to a cream oil. Purification by column chromatography (silica gel, 5% MeOH/CH₂Cl₂) afforded the title compound **29** (0.59 g, 1.65 mmol, 94%) as a colorless oil: [α]_D²⁷ -10.1 (c 0.44, CHCl₃); IR $\nu_{\max}$ (neat) 3360, 2956, 2923, 2853 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 5.52–5.36 (2H, m), 4.05 (1H, td, *J* = 6.8, 3.9 Hz), 3.89 (1H, td, *J* = 6.8, 4.5 Hz), 3.75–3.69 (2H, m), 3.59 (1H, m), 3.50 (1H, m), 3.13 (1H, br s), 2.53 (1H, br s), 2.42 (1H, br s), 2.26–2.05 (2H, m), 2.03–1.85 (6H, m), 1.66–1.48 (2H, m), 1.38–1.22 (16H, m), 0.89 (3H, t, *J* = 6.9 Hz) ppm; ¹³C NMR (100 MHz, CDCl₃) δ 131.4, 129.3, 82.8, 80.5, 73.7, 73.6, 65.2, 34.3, 32.6, 31.9, 29.6, 29.6, 29.5, 29.3, 29.2, 28.8, 28.1, 28.0, 22.7, 14.1 ppm; LRMS (ES⁺) *m/z* 735 379 ([M + Na]⁺); HRMS (ES⁺) for C₂₁H₄₀O₄Na⁺, calcd 379.2819, found 379.2813.

(1S,4E)-1-((2S,5R)-5-((4R)-2,2-Dimethyl-1,3-dioxolan-4-yl)-tetrahydrofuran-2-yl)-pentadec-4-en-1-ol (31). To a solution of triol **29** (326 mg, 0.91 mmol) in 2,2-dimethoxypropane (15 mL) was added *p*-TsOH (20 mg), and the resulting mixture was stirred for 2.5 h. The solution was diluted with EtOAc (30 mL) and washed with H₂O (10 mL), saturated aqueous NaHCO₃ (2 × 10 mL), and brine (20 mL). The organic phase was dried (Na₂SO₄) and concentrated in vacuo to a colorless oil. Purification by column chromatography (silica gel, 20% EtOAc/hexane) afforded the title compound **31** (333 mg, 0.84 mmol, 92%) as a colorless oil: [α]_D²⁷ +1.3 (c 0.39, CHCl₃); IR $\nu_{\max}$ (neat) 3476, 2923, 2853 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 5.45 (1H, dt, *J* = 15.3, 5.6 Hz), 5.40 (1H, dt, *J* = 15.3, 5.6 Hz), 4.11 (1H, ddd, *J* = 7.6, 6.5, 4.8 Hz), 4.02–3.95 (1H, m), 4.01 (1H, t, *J* = 7.6 Hz), 3.91–3.85 (1H, m), 3.78 (1H, t, *J* = 7.6 Hz), 3.46–3.39 (1H, m), 2.60 (1H, d, *J* = 6.5 Hz), 2.26–2.04 (2H, m), 2.02–1.89 (4H, m), 1.86–1.76 (2H, m), 1.63–1.48 (2H, m), 1.45 (3H, s), 1.38 (3H, s), 1.36–1.22 (16H, m), 0.89 (3H, t, *J* = 6.9 Hz) ppm; ¹³C NMR (100 MHz, CDCl₃) δ 131.0, 129.6, 109.6, 82.8, 79.1, 78.0, 73.8, 66.2, 34.1, 32.6, 31.9, 29.6, 29.6, 29.5, 29.3, 29.2, 28.7, 28.1, 28.0, 26.4, 25.5, 22.7, 14.1 ppm; LRMS (ES⁺) *m/z* 419 ([M + Na]⁺), 414 ([M+NH₄]⁺); HRMS (ES⁺) for C₂₄H₄₄O₄Na⁺, calcd 419.3132, found 419.3132.

(1S,4S,5S)-1-((2S,5R)-5-((4R)-2,2-Dimethyl-1,3-dioxolan-4-yl)-tetrahydrofuran-2-yl)-4,5-dihydroxypentadecan-1-ol (39). To an orange biphasic mixture of H₂O (10 mL), ^tBuOH (10 mL), ADMIX α (2.00 g), and MeSO₂NH₂ (0.08 g, 0.84 mmol) at 0 °C was added mono-THF **31** (0.33 g, 0.84 mmol) in Et₂O (3 mL) and ^tBuOH (3 mL). The resulting orange mixture was stirred for 15 h before it was quenched with Na₂SO₃ (2.00 g) and then stirred for a further 30 min. H₂O (15 mL) was added, and the aqueous phase extracted with EtOAc (4 × 20 mL). The combined organic phases were washed with 2 M KOH (3 × 15 mL), dried (Na₂SO₄), and concentrated in vacuo to an orange oil. Purification by column chromatography (silica gel, 5% MeOH/CH₂Cl₂) afforded the title compound **39** (0.34 g, 0.79 mmol, 94%) as a colorless oil: [α]_D²⁷ +1.44 (c 0.52, CHCl₃); IR $\nu_{\max}$ (neat) 3408, 2922, 2853 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 4.10 (1H, ddd, *J* = 7.5, 6.3, 4.5), 4.03–3.97 (1H, m), 4.01 (1H, t, *J* = 7.5 Hz), 3.92–3.86 (1H, m), 3.78 (1H, t, *J* = 7.5 Hz), 3.53 (1H, br s), 3.51–3.37 (3H, m), 3.19 (1H, br s), 2.29 (1H, d, *J* = 4.8 Hz), 2.03–1.92 (2H, m), 1.86–1.78 (2H, m), 1.77–1.57 (4H, m), 1.54–1.42 (2H, m), 1.46 (3H, s), 1.38 (3H, s), 1.34–1.21 (16H, m), 0.89 (3H, t, *J* = 6.9 Hz) ppm; ¹³C NMR (100 MHz, CDCl₃) δ 109.6, 82.9, 79.1, 78.0, 74.8, 74.3, 66.2, 33.7, 31.9, 30.8, 30.7, 29.7, 29.6, 29.3, 28.2, 28.0, 26.5, 25.7, 25.5, 22.7, 14.1 ppm; LRMS (ES⁺) *m/z* 453 ([M + Na]⁺), 431 ([M + H]⁺); HRMS (ES⁺) for C₂₄H₄₆O₆Na⁺, calcd 453.3187, found 453.3180.

(1R)-1-((2R,5S)-5-((2S,5R)-5-((1S)-1-Hydroxyundecyl)-tetrahydrofuran-2-yl)-tetrahydrofuran-2-yl)-ethane-1,2-diol (37). By the *ortho*-ester cyclization method: To a solution of mono-THF acetal **39** (57 mg, 0.13 mmol) and trimethylorthoacetate (19 mg, 0.16 mmol) in CH₂Cl₂ (2 mL) at 0 °C was added BF₃·OEt₂ (2 mg, 0.01 mmol), and the resulting mixture was warmed to room temperature after 1 h. After 35 h acetone (1 mL) was added, and the mixture was concentrated in vacuo to a colorless oil. The crude oil was redissolved in MeOH (3 mL) before K₂CO₃ (74 mg, 0.52 mmol) was added, and the mixture was stirred for 4 h before concentrating in vacuo to a white solid. Purification by column chromatography (silica gel, 5% MeOH/CH₂Cl₂) afforded the title compound **37** (34 mg, 0.09 mmol, 71%) as a colorless gum: [α]_D²⁷ +0.6 (c 1.05, CHCl₃); IR $\nu_{\max}$ (neat) 3404, 2923, 2853 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 4.14 (1H, td, *J* = 6.0, 3.1 Hz), 4.03–3.97 (1H, m), 3.93–3.83 (3H, m), 3.79–3.66 (3H, m), 3.57–3.50 (1H, m), 3.33 (1H, br s), 2.85 (1H, dd, *J* = 8.0, 4.0 Hz), 2.06–1.71 (8H, m), 1.41–1.23 (18H, m), 0.89 (3H, t, *J* = 6.9 Hz) ppm; ¹³C NMR (100 MHz, CDCl₃) δ 83.2, 81.6, 80.9, 80.7, 73.5, 71.5, 65.7, 33.1, 31.9, 29.7, 29.6, 29.6, 29.3, 28.6, 28.4, 28.3, 26.0, 23.4, 22.7, 14.1 ppm; LRMS (ES⁺) *m/z* 395 ([M + Na]⁺), 373 ([M + H]⁺); HRMS (ES⁺) for C₂₁H₄₀O₅Na⁺, calcd 395.2768, found 395.2762.

(2R)-2-((2R,5S)-5-((2S,5R)-((1S)-1-Hydroxyundecyl)-tetrahydrofuran-2-yl)-tetrahydrofuran-2-yl)-2-hydroxyethyl-4-methylbenzenesulphonate (45). To a solution of triol **37** (197 mg, 0.53 mmol) in benzene (12 mL) was added Bu_2SnO (158 mg, 0.63 mmol), and the resulting mixture was heated under reflux for 3 h. The cloudy white solution was then cooled to room temperature before TsCl (111 mg, 0.58 mmol) and TBAB (85 mg, 0.26 mmol) were added. The mixture was stirred for 1.5 h and then concentrated in vacuo to a white oil. Purification by column chromatography (silica gel, 40% $\rightarrow$ 60% EtOAc/hexane) afforded the title compound **45** (272 mg, 0.52 mmol, 97%) as a colorless gum: $[\alpha]_D^{27} +0.2$ (c 0.68, CHCl_3); IR ν_{max} (neat) 3411, 2923, 2853, 1189, 1176 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.81 (2H, d, $J = 8.1$ Hz), 7.34 (2H, d, $J = 8.1$ Hz), 4.09–4.01 (3H, m), 3.92 (1H, td, $J = 6.8, 3.8$ Hz), 3.87–3.78 (3H, m), 3.70 (1H, ddt, $J = 3.0, 8.0, 6.0$ Hz), 3.45 (1H, d, $J = 7.0$ Hz), 3.60 (1H, s), 2.45 (3H, s), 2.02–1.70 (8H, m), 1.53–1.21 (18H, m), 0.89 (3H, t, $J = 6.9$ Hz) ppm; ^{13}C NMR (100 MHz, CDCl_3) δ 144.7, 133.0, 129.8, 128.0, 83.0, 81.0, 80.6, 78.6, 71.7, 71.4, 71.1, 33.2, 31.9, 30.9, 29.7, 29.6, 29.6, 29.3, 28.5, 28.4, 27.7, 25.9, 23.7, 22.7, 21.6, 14.1 ppm; LRMS (ES^+) m/z 549 $[\text{M} + \text{Na}]^+$, 527 $[\text{M} + \text{H}]^+$; HRMS (ES^+) for $\text{C}_{28}\text{H}_{46}\text{O}_7\text{SNa}^+$, calcd 549.2856, found 549.2846.

(1S)-1-((1R,5S)-5-((2S,5R)-5-((1R)-Oxiran-2-yl)-tetrahydrofuran-2-yl)-tetrahydrofuran-2-yl)-undecan-1-ol (46). To a solution of tosylate **45** (202 mg, 0.38 mmol) in MeOH (14 mL) was added K_2CO_3 (58 mg, 0.42 mmol), and the resulting cloudy mixture was stirred for 2 h and then concentrated in vacuo to a white solid. Purification by column chromatography (silica gel, 40% EtOAc/hexane) afforded the title compound **46** (109 mg, 0.31 mmol, 81%) as a colorless gum: $[\alpha]_D^{27} +1.7$ (c 0.30, CHCl_3); IR ν_{max} (neat) 3477, 2923, 2853, 1466 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 3.95–3.83 (5H, m), 3.03 (1H, q, $J = 3.5$ Hz), 2.78 (1H, br), 2.75 (2H, d, $J = 3.5$ Hz), 2.07–1.70 (8H, m), 1.53–1.21 (18H, m), 0.89 (3H, t, $J = 6.9$ Hz) ppm; ^{13}C NMR (100 MHz, CDCl_3) δ 82.8, 81.6, 81.0, 78.6, 71.8, 53.7, 44.1, 32.7, 31.9, 29.7, 29.6, 29.6, 29.3, 28.5, 28.4, 28.1, 26.0, 23.7, 22.7, 14.1 ppm; LRMS (ES^+) m/z 377 $[\text{M} + \text{Na}]^+$, 372 $[\text{M} + \text{NH}_4]^+$; HRMS (ES^+) for $\text{C}_{21}\text{H}_{38}\text{O}_4\text{Na}^+$, calcd 377.2662, found 377.2661.

(1R)-1-((2R,5S)-5-((2S,5R)-5-((1S)-1-Hydroxyundecyl)-tetrahydrofuran-2-yl)-tetrahydrofuran-2-yl)-undec-10-en-1-ol (47). Mg turnings (95 mg, 3.90 mmol) were heated to 400 °C for 10 min and then allowed to cool to room temperature. THF (9 mL) and I_2 (1 crystal) were added followed by the dropwise addition of 1-bromononene (50 mg, 0.24 mmol). The resulting orange solution was heated to reflux until the orange color disappeared (~ 5 min) before the remaining 1-bromononene (500 mg, 2.44 mmol) was added. The mixture was heated under reflux for a further 1 h. Titration of this solution using I_2 gave an average concentration of 0.28 M. An aliquot of this solution (2.5 mL, 0.69 mmol) was added to a suspension of CuBr (25 mg, 0.17 mmol) in THF (3 mL) at -60 °C, and the resulting gray solution was warmed to -30 °C over 1 h. The mixture was allowed to stir at this temperature for a further 30 min. The reaction mixture was then cooled to -60 °C before epoxide **46** (41 mg, 0.12 mmol) in THF (1 mL) was added dropwise. The resulting mixture was warmed to -40 °C over 1 h before quenching with saturated aqueous NH_4Cl (3 mL) and aqueous NH_3 (1 mL) and extracted with EtOAc (4×5 mL). The combined organic phases were dried (Na_2SO_4) and concentrated in vacuo. Purification by column chromatography (silica gel, 20% $\rightarrow$ 40% EtOAc/hexane) afforded the title compound **47** (42 mg, 0.09 mmol, 75%) as a colorless gum: $[\alpha]_D^{27} +15.8$ (c 0.65, CHCl_3); IR ν_{max} (neat) 3437, 2922, 2852 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 5.81 (1H, ddt, $J = 17.1, 10.3, 6.7$ Hz), 4.99 (1H, dq, $J = 17.1, 1.8$ Hz), 4.93 (1H, ddt, $J = 10.3, 2.3, 1.2$ Hz), 3.95–3.80 (5H, m), 3.46–3.37 (1H, m), 2.93 (1H, br s), 2.83 (1H, br d, $J = 5.0$ Hz), 2.08–2.01 (2H, m), 2.01–1.74 (8H, m), 1.54–1.42 (2H, m), 1.42–1.21 (30H, m), 0.89 (3H, t, $J = 6.9$ Hz) ppm; ^{13}C NMR (100 MHz, CDCl_3) δ 139.2, 114.1, 83.1, 82.9, 81.1, 81.0, 74.0, 71.9,

34.3, 33.8, 32.8, 31.9, 29.7, 29.6, 29.6, 29.4, 29.3, 29.1, 28.9, 28.8, 28.4, 27.9, 26.0, 25.8, 23.8, 22.7, 14.1 ppm; LRMS (ES^+) m/z 503 $[\text{M} + \text{Na}]^+$, 481 $[\text{M} + \text{H}]^+$; HRMS (ES^+) for $\text{C}_{30}\text{H}_{56}\text{O}_4\text{Na}^+$, calcd 503.4071, found 503.4073.

(5S)-3-((11R,2E)-11-Hydroxy-11-((2R,5S)-5-((2S,5R)-5-((1S)-1-hydroxyundecyl)-tetrahydrofuran-2-yl)-tetrahydrofuran-2-yl)undec-2-enyl)-5-methylfuran-2(5H)-one (48). To a solution of alkene **47** (42 mg, 90 mmol) and propargylic alcohol **24** (14 mg, 96 mmol) in DMF (2 mL) was added $\text{CpRu}(\text{MeCN})_3\text{PF}_6$ (4 mg, 9 mmol). The resulting orange mixture was allowed to stir for 2 h and then filtered through a plug of silica (60% EtOAc/hexane). Purification by column chromatography (silica gel, 1% $\rightarrow$ 2% $\text{MeOH/CH}_2\text{Cl}_2$) afforded the title compound **48** (28 mg, 49 mmol, 55%) as an orange oil: $[\alpha]_D^{27} +19.6$ (c 0.45, CHCl_3); IR ν_{max} (neat) 3448, 2923, 2853, 1757 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 6.99 (1H, q, $J = 1.9$ Hz), 5.58 (1H, dt, $J = 15.1, 6.5$ Hz), 5.46 (1H, dtt, $J = 15.3, 6.5, 1.3$ Hz), 5.01 (1H, qq, $J = 6.4, 1.9$ Hz), 3.95–3.81 (5H, m), 3.42 (1H, dt, $J = 7.5, 4.2$ Hz), 2.96 (2H, d, $J = 6.5$ Hz), 2.86 (2H, br s), 2.07–1.99 (2H, m), 1.99–1.71 (8H, m), 1.55–1.43 (2H, m), 1.42 (3H, d, $J = 6.4$ Hz), 1.39–1.20 (28H, m), 0.89 (3H, t, $J = 6.9$ Hz) ppm; ^{13}C NMR (100 MHz, CDCl_3) δ 173.5, 149.3, 134.1, 133.6, 124.3, 83.0, 82.9, 81.1, 80.9, 77.6, 74.0, 72.0, 34.3, 32.8, 32.5, 31.9, 29.7, 29.6, 29.6, 29.4, 29.3, 29.3, 29.1, 28.8, 28.4, 27.9, 26.0, 25.8, 23.8, 22.7, 19.2, 14.1 ppm; LRMS (ES^+) m/z 1175 $[\text{2M} + \text{Na}]^+$, 599 $[\text{M} + \text{Na}]^+$, 594 $[\text{M} + \text{NH}_4]^+$; HRMS (ES^+) for $\text{C}_{35}\text{H}_{60}\text{O}_6\text{Na}^+$, calcd 599.4282, found 599.4286.

Membranollin (2). To a solution of bis-THF **48** (28 mg, 49 mmol) and TsNHNH_2 (91 mg, 490 mmol) in THF (4 mL) was added a solution of NaOAc (40 mg, 490 mmol) in H_2O (4 mL). The resulting mixture was heated at reflux for 29 h before further TsNHNH_2 (45 mg, 245 mmol) and NaOAc (20 mg, 245 mmol) were added. The mixture was heated to reflux for a further 18 h, cooled to room temperature, and diluted with H_2O (2 mL). The aqueous phase was extracted with Et_2O (5×4 mL), and the combined organic phases were dried (Na_2SO_4) and concentrated in vacuo to a colorless oil. Purification by column chromatography (silica gel, 0 $\rightarrow$ 1% $\text{MeOH/CH}_2\text{Cl}_2$) afforded the title compound **2** (19 mg, 33 mmol, 68%) as a colorless oil, which solidified to give a waxy solid: $[\alpha]_D^{27} +23.5$ (c 0.95, CHCl_3) and $+27.1$ (c 0.51, MeOH)³⁶ [lit.^{4c} $+10$ (c 0.8, MeOH)]; mp 43–45 °C (no reported mp); IR ν_{max} (neat) 3444, 2924, 2853, 1757 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 3.99 (1H, appt q, $J = 1.7$ Hz), 4.99 (1H, qq, $J = 6.8, 1.7$ Hz), 3.95–3.81 (5H, m), 3.45–3.39 (1H, m), 2.89 (2H, br m), 2.27 (2H, tt, $J = 7.8, 1.6$ Hz), 2.01–1.72 (8H, m), 1.60–1.39 (4H, m), 1.41 (3H, d, $J = 6.8$ Hz), 1.38–1.22 (32H, m), 0.89 (3H, t, $J = 6.9$ Hz) ppm; ^{13}C NMR (100 MHz, CDCl_3) δ 173.8, 148.8, 134.4, 83.1, 82.9, 81.1, 81.0, 77.4, 74.0, 72.0, 34.3, 32.8, 31.9, 29.7, 29.6, 29.6, 29.5, 29.3, 29.2, 28.8, 28.5, 27.9, 27.4, 26.0, 25.8, 25.2, 23.8, 22.7, 19.2, 14.1 ppm; LRMS (ES^+) m/z 601 $[\text{M} + \text{Na}]^+$, 579 $[\text{M} + \text{H}]^+$; HRMS (ES^+) for $\text{C}_{35}\text{H}_{62}\text{O}_6\text{Na}^+$, calcd 601.4439, found 601.4422.

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Supporting Information Available: Experimental procedures and spectroscopic data for compounds **9–14**, **15a–20a**, **15b–20b**, **ent-20b**, **21–23**, **25**, **26**, **30**, **32–36**, **38**, and **40–44**; copies of NMR spectra for new compounds; details of stereochemical assignment for derivatives (Mosher's esters) of compounds **21**, **22**, and **33**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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