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Total Synthesis and Stereochemical Assignment of *cis*-Uvariamicin I and *cis*-Reticulatacin

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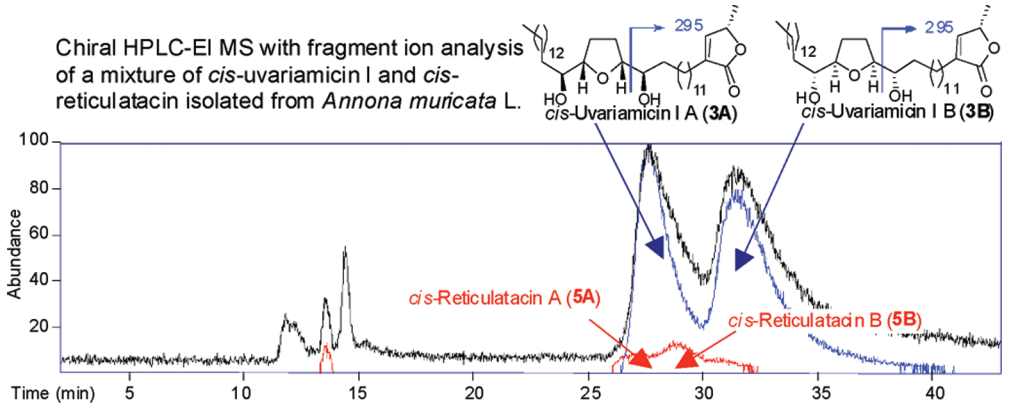

Diastereoisomeric mixtures of *cis*-uvariamicin I (15*R*,16*R*,19*S*,20*S*,36*S* and 15*S*,16*S*,19*R*,20*R*,36*S*) and *cis*-reticulatacin (17*R*,18*R*,21*S*,22*S*,36*S* and 17*S*,18*S*,21*R*,22*R*,36*S*) were synthesized to determine the stereochemistry of the natural products isolated from *Annona muricata*. It was not possible to resolve a mixture of the four synthetic isomers using chiral HPLC, but the mixed isomers could be distinguished using chiral HPLC EIMS with extracted fragment ion analysis. Comparison of synthetic standards with the natural isolate revealed that *cis*-uvariamicin I and *cis*-reticulatacin are present in nature as mixtures of *threo-cis-threo* diastereoisomers. It is suggested that the nomenclature for the natural products is amended as follows: (15*R*,16*R*,19*S*,20*S*,36*S*)-*cis*-uvariamicin I (*cis*-uvariamicin IA); (15*S*,16*S*,19*R*,20*R*,36S)-*cis*-uvariamicin I (*cis*-uvariamicin IB); (17*R*,18*R*,21*S*,22*S*,36*S*)-*cis*-reticulatacin (*cis*-reticulatacin A); (17*S*,18*S*,21*R*,22*R*,36*S*)-*cis*-reticulatacin (*cis*-reticulatacin B).

Introduction

Annonaceous acetogenins are a substantial group of bioactive natural products isolated from plants belonging to the Annonaceae family.[1] Structuraly, these acetogenins derive from C_{32} or C_{34} unbranched fatty acids and frequently share several features including 2,5-disubstituted tetrahydrofuran rings, secondary alcohol groups, and a butenolide or lactone ring. Despite these structural similarities, stereochemical and positional diversity means that in excess of 400 annonaceous acetogenins are known.[1a]

Due to their waxy physical nature, structural determination of annonaceous acetogenins by X-ray diffraction has rarely been possible.[2] As a consequence, stereochemical

(1) Reviews of the chemistry and biology of Annonaceous acetogenins: (a) Bermejo, A.; Figadère, B.; Zafra-Polo, M. C.; Barrachina, I.; Estornell, E.; Cortes, D. *Nat. Prod. Rep.* **2005**, *22*, 269–303. (b) Alali, F. Q.; Liu, X. X.; McLaughlin, J. L. *J. Nat. Prod.* **1999**, *62*, 504–540. (c) Zeng, L.; Ye, Q.; Oberlies, N. H.; Shi, G.; Gu, Z. M.; He, K.; McLaughlin, J. L. *Nat. Prod. Rep.* **1996**, *13*, 275–306. (d) Zafra-Polo, M. C.; Figadere, B.; Gallardo, T.; Tormo, J. R.; Cortes, D. *Phytochemistry* **1998**, *48*, 1087–1117. (e) Saez, J.; Sahpaz, S.; Villaescusa, L.; Hocquemiller, R.; Cavé, A.; Cortes, D. *J. Nat. Prod.* **1993**, *56*, 351–356. (f) Rupprecht, J. K.; Hui, Y. H.; McLaughlin, J. L. *J. Nat. Prod.* **1990**, *53*, 237–278.

(2) (a) Yu, J. G.; Hu, X. F. E.; Ho, D. K.; Bean, M. F.; Stephens, R. E.; Cassady, J. M.; Brinen, L. S.; Clardy, J. *J. Org. Chem.* **1994**, *59*, 1598–1599. (b) Pettit, G. R.; Cragg, G. M.; Polonsky, J.; Herald, D. L.; Goswami, A.; Smith, C. R.; Moretti, C.; Schmidt, J. M.; Weisleder, D. *Can. J. Chem.-Rev. Can. Chim.* **1987**, *65*, 1433–1435.

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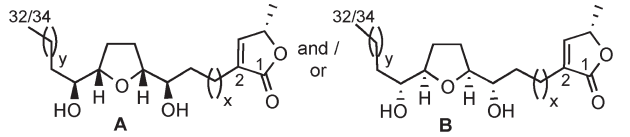


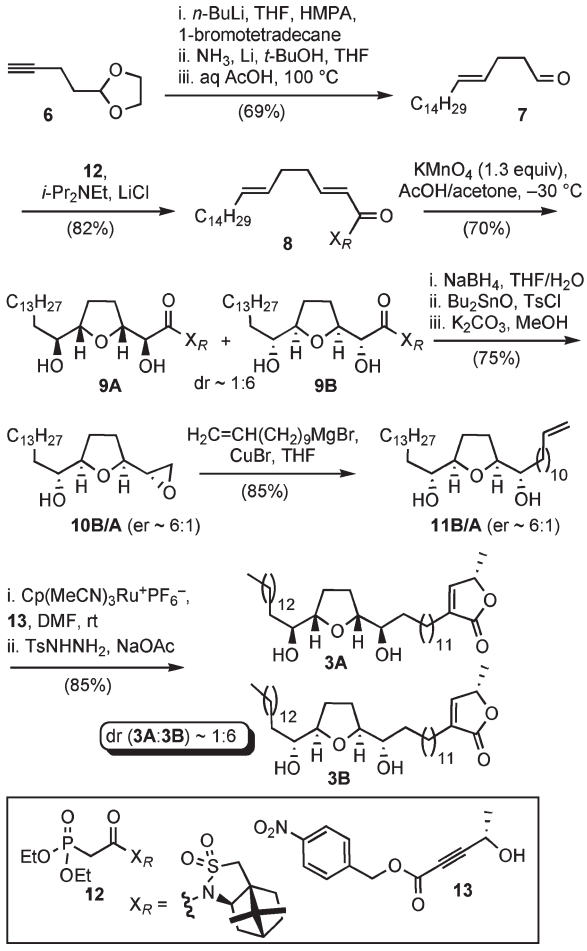
FIGURE 1. Structures of selected mono-THF acetogenins isolated from *Annona muricata* L. $^{\Psi}$*cis*-uvariamicin I and *cis*-reticulatacin isolated together as a mixture.

assignment within the THF-containing regions has relied upon analysis of NMR data from the natural products and their derivatives.[3−5] The position of THF rings along the carbon backbone can be readily deduced from EIMS fragmentation patterns. However, additional synthesis and fragmentation of unsymmetrical derivatives may be necessary to determine which chain is connected to which side of a central mono- or bis-THF unit.[4a] Comparison of spectroscopic data from the natural products with data collected from samples prepared by total synthesis might have been expected to answer these stereochemical issues, but certain groups of stereoisomeric acetogenins give "substantially identical" ^{1}H and ^{13}C NMR spectra.[5,6] In the present work, we show how the structures of a mixture of four isomeric acetogenins can be deduced by comparison of synthetic standards with the natural isolate using chiral HPLC linked to EIMS with extracted fragment ion analysis.

Seven mono-THF acetogenins, including *cis*-solamin (**1**), *cis*-uvariamicin I (**3**), and *cis*-reticulatacin (**5**), were isolated from the roots of a tropical fruit tree *Annona muricata* L. (Figure 1).[7] On the basis of their NMR chemical shift data, six of these acetogenins, including **1**−**5**, were shown to contain *threo-cis-threo* configured 2,5-bis(hydroxyalkyl)-tetrahydrofuran (THF-diol) motifs. However, only the relative stereochemistry of the THF-diol could be determined due to local symmetry within these molecules. Through total synthesis of both likely *threo-cis-threo* diastereoisomers of *cis*-solamin and chiral HPLC analysis, we discovered that natural *cis*-solamin had actually been isolated as a mixture of the two possible *threo-cis-threo* diastereoisomers [*cis*-solamin A (**1A**) and *cis*-solamin B (**1B**)].[6]

We were intrigued whether this observation extended to other mono-THF acetogenins. The stereochemical assignment of *cis*-uvariamicin I (**3**) and *cis*-reticulatacin (**5**) presented an exceptional challenge due not only the possible existence of two stereoisomers **A/B** for each but also to the fact that these structural isomers **3** and **5** had not been separated during isolation. To resolve this puzzle, we decided to synthesize both natural products as predefined mixtures of *threo-cis-threo* isomers **3A/B** and **5A/B** and then use the synthetic mixtures to facilitate the analysis of the natural isolate using chiral HPLC.

SCHEME 1. Synthesis of *cis*-Uvariamicin I Diastereoisomers 3A/B



Results and Discussion

The synthesis of *cis*-uvariamicin I (**3**) was tackled first using the permanganate-mediated oxidative cyclization of (*E*,*E*)-1,5-dienoyl system **8** to secure the *threo-cis-threo*-configured THF-diol core (Scheme 1).[6] The (2*R*)-camphor sultam auxiliary was used to impart diastereofacial bias in the oxidative cyclization, thereby delivering a separable mixture of THF-diols **9A** and **9B** (dr ∼ 1:6).[8] This diastereoisomeric mixture was used in the subsequent steps so that *cis*-uvariamicin I was ultimately obtained as a mixture of two diastereoisomers **3A** and **3B** in an approximate ratio of 1:6. As anticipated, the fact that a mixture of *cis*-uvariamicin I diastereoisomers had been synthesized was not apparent from inspection of ^{1}H or ^{13}C NMR spectra, with only one set of signals observed. Furthermore, physical and spectroscopic data recorded for

(3) Analysis of relative stereochemistry by NMR: (a) Hoye, T. R.; Suhadolnik, J. C. *J. Am. Chem. Soc.* **1987**, *109*, 4403–4404. (b) Hoye, T. R.; Zhuang, Z. P. *J. Org. Chem.* **1988**, *53*, 5578–5580. (c) Born, L.; Lieb, F.; Lorentzen, J. P.; Moeschler, H.; Nonfon, M.; Sollner, R.; Wendisch, D. *Planta Med.* **1990**, *56*, 312–316. (d) Fujimoto, Y.; Murasaki, C.; Shimada, H.; Nishioka, S.; Kakinuma, K.; Singh, S.; Singh, M.; Gupta, Y. K.; Sahai, M. *Chem. Pharm. Bull.* **1994**, *42*, 1175–1184.

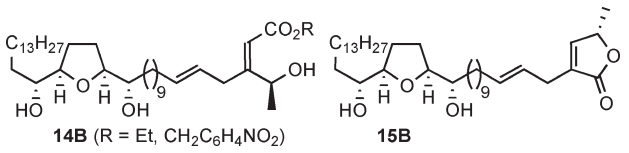
(4) Application of Mosher's ester derivatives of Annonaceous acetogenins: (a) Rieser, M. J.; Hui, Y. H.; Rupprecht, J. K.; Kozlowski, J. F.; Wood, K. V.; McLaughlin, J. L.; Hanson, P. R.; Zhuang, Z. P.; Hoye, T. R. *J. Am. Chem. Soc.* **1992**, *114*, 10203–10213. (b) Hoye, T. R.; Jeffrey, C. S.; Shao, F. *Nature Protoc.* **2007**, *2*, 2451–2458.

(5) Curran, D. P.; Zhang, Q. S.; Lu, H. J.; Gudipati, V. *J. Am. Chem. Soc.* **2006**, *128*, 9943–9956.

(6) (a) Cecil, A. R. L.; Hu, Y.; Vicent, M. J.; Duncan, R.; Brown, R. C. D. *J. Org. Chem.* **2004**, *69*, 3368–3374. (b) Hu, Y. L.; Cecil, A. R. L.; Frank, X.; Gleye, C.; Figadere, B.; Brown, R. C. D. *Org. Biomol. Chem.* **2006**, *4*, 1217–1219.

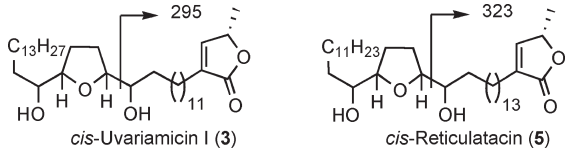
(7) Gleye, C.; Duret, P.; Laurens, A.; Hocquemiller, R.; Cavé, A. *J. Nat. Prod.* **1998**, *61*, 576–579.

(8) The diastereoisomers were separated for characterization, then recombined.



14B (R = Et, $CH_2C_6H_4NO_2$) **15B**

FIGURE 2. Ruthenium-catalyzed Alder−ene reaction products **14B** and **15B** (major diastereoisomers shown).



cis-Uvariamicin I (**3**) *cis*-Reticulatacin (**5**)

FIGURE 3. Characteristic EIMS fragment ions for **3** and **5**.

our mixture were in excellent agreement with data reported for the mixture of *cis*-uvariamicin I and *cis*-reticulatacin isolated from *Annona muricata* L.[7]

The synthesis of the butenolide ring system deserves some comment because the regioisomeric addition byproduct **14** (R = Et) obtained from the Trost Alder−ene reaction, between **11A/11B** and (*S*)-ethyl 4-hydroxypent-2-ynoate, proved very difficult to separate from the desired butenolide **15** (Figure 2). The commercially available catalyst $Cp(CH_3CN)_3RuPF_6$[9] gave some advantage in terms of regioselectivity over CpRu(cod)Cl (**15**:**14** ∼ 10:1),[10] but a significant quantity of the regioisomer was still present. Changing the alkyne ester group to 4-nitrobenzyl ultimately permitted separation of the desired Alder−ene product from the regioisomeric addition byproduct **14**.

The total synthesis of a mixture of *cis*-reticulatacin stereoisomers **5A**/**5B** (dr ∼ 1:8)[8] was accomplished similarly in 11 steps and 17% overall yield from alkyne **6**. ^1H and ^{13}C NMR data for **5A**/**5B** were consistent with those reported for the natural isolate and very similar to those obtained for synthetic *cis*-uvariamicin I.[7,11]

Chiral HPLC analysis of the synthetic samples using a CD-Ph column allowed us to achieve baseline separation of the *cis*-uvariamicin I diastereoisomers (**3A**/**3B**, ∼1:6 mixture) and near baseline separation of the *cis*-reticulatacin diastereoisomers (**5A**/**5B**, ∼1:8 mixture).[12] However, it was not possible to fully resolve the mixture obtained after the four synthetic isomers (**3A**/**3B** and **5A**/**5B**) were combined, with only three peaks being evident in the HPLC chromatogram (UV detection at 214 nm). Furthermore, chiral HPLC analysis of the natural isolate (*cis*-uvariamicin I + *cis*-reticulatacin) showed only two peaks. These two peaks corresponded to **3A** and **3B** rather than **3A/B** and **5A/B**, an observation that was consistent with the presence of *cis*-reticulatacin as a minor component in the natural isolate.

Fortunately, the structural isomers **3** and **5** are distinguished on the basis of their EIMS fragment ions *m*/*z* 295 and 323, respectively (Figure 3). It was possible to analyze

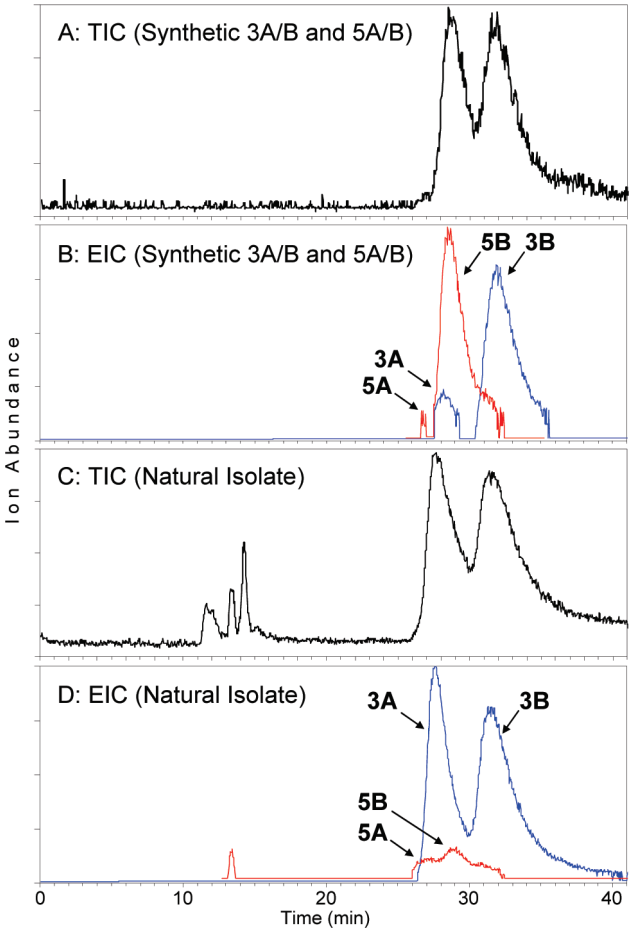


FIGURE 4. Reconstructed chromatograms for a mixture of synthetic **3A**/**B** and **5A**/**B** (traces A and B), and the natural isolate (traces C and D).

the effluent from the chiral column by EIMS, enabling reconstruction of chromatograms using the total ion and extracted ion currents (TIC and EIC) for the two fragment ions (Figure 4). Four peaks could then be visualized for the mixture of synthetic standards using the reconstructed chromatograms. Furthermore, the natural isolate clearly showed two peaks corresponding to uvariamicin I isomers (**3A** and **3B**) in approximately equal amounts (blue trace). Also evident were two weak peaks (red trace), which corresponded to the reticulatacin isomers (**5A** and **5B**), thereby showing that the natural isolate was in fact a mixture of structural and stereoisomers.[12,13]

In summary, we have determined that natural *cis*-uvariamicin I and *cis*-reticulatacin, isolated from *Annona muricata* L., are each mixtures of both possible *threo-cis-threo* diastereoisomers. We believe that it is likely that other related mono-THF acetogenins, which possess the same relative configuration in their THF diol cores, are also mixtures of diastereoisomers. For *cis*-solamin, *cis*-uvariamicin I, and *cis*-reticulatacin we have found it to be convenient to refer to the diastereoisomers with *R*,*R*,*S*,*S*- and *S*,*S*,*R*,*R*-configured THF cores as A and B, respectively (i.e., (17*R*,18*R*,21*S*,22*S*,36*S*)-*cis*-reticulatacin is

(9) Trost, B. M.; Toste, F. D. *Tetrahedron Lett.* **1999**, *40*, 7739–7743.
(10) Exclusive formation of the desired butenolide has been reported for a very similar substrate: Goksel, H.; Stark, C. B. W. *Org. Lett.* **2006**, *8*, 3433–3436.
(11) ^1H and ^{13}C NMR data are compared in the Supporting Information.
(12) See the Supporting Information for copies of HPLC chromatograms.
(13) The results were further supported by collecting fractions from the chiral HPLC and analyzing the individual fractions using APCI MS (see the Supporting Information).

cis-reticulatacin A). It is suggested that, where possible, a similar nomenclature is applied to other mono-THF acetogenins possessing *threo-cis-threo*-configured THF-diol core units when the absolute stereochemistry of the core is in doubt. However, some caution should be exercised due to the existing use of letters in the names for certain acetogenins.[1a]

Experimental Section

Oxidative Cyclization Products 9A and 9B. At −30 °C, powdered $KMnO_4$ (221 mg, 1.40 mmol) was added in one batch to a rapidly stirred solution of diene **8** (520 mg, 1.00 mmol) in AcOH/acetone (25 mL, 2:3). The reaction mixture was allowed to warm to −10 °C over 1 h, whereupon ice-cold saturated aqueous $Na_2S_2O_5$ (20 mL) was added followed by EtOAc (40 mL). The organic phase was separated,and the aqueous layer was re-extracted with EtOAc (3 × 20 mL). The combined organic extracts were dried ($MgSO_4$), and solvents were removed in vacuo to give a yellow oil. Purification by column chromatography (silica gel, Et_2O/hexane 1:4 → 3:2) gave the title THF-diols a two separate diastereoisomers (**9A** and **9B** combined: 399 mg, 0.7 mmol, 70%) as gummy oil. The two diastereoisomers were separated, and after all the required physical and analytical data were collected, the two separated diastereoisomers were mixed to form an approximately 6:1 mixture of **9B** and **9A**, respectively. **Data for 9B** (syrup): $[\alpha]^{26}_D$ −20.5 ($CHCl_3$, *c* 0.39); IR (neat) 2922, 1690, 1332, 1272, 1218, 1136, 1111 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.60−4.54 (2H, m), 4.05 (1H, br, m), 3.96 (1H, dd, J = 5.1, 7.5 Hz), 3.87 (1H, dt, J = 4.6, 7.1 Hz), 3.51 (1H, d, J = 13.8 Hz), 3.48−3.43 (1H, m), 3.43 (1H, d, J = 13.8 Hz), 2.30−2.21 (1 H, m), 2.14−2.00 (3H, m), 1.98−1.70 (5H, m), 1.55−1.20 (28H, m), 1.15 (3H, s), 0.97 (3H, s), 0.88 (3H, t, J = 6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.8, 83.3, 78.7, 74.0, 73.6, 65.9, 53.1, 49.1, 47.9, 44.7, 38.3, 34.6, 33.0, 32.0, 29.4, 28.4, 28.2, 26.5, 25.9, 22.7, 20.9 19.9, 14.2; LRMS (ES^+) *m*/*z* 1161 592 ($[M + Na]^+$), 570 ($[M + H]^+$). Data for **9A** are included in the Supporting Information.

(*S*)-1-((2*S*,5*R*)-5-((*R*)-1-Hydroxypentadecyl)tetrahydrofuran-2-yl)ethane-1,2-diol (er ∼ 6:1). To a solution of **9A/9B** (1.52 g, 2.72 mmol, dr ∼ 1:6) in THF (80 mL) and H_2O (5 mL) at −10 °C was added $NaBH_4$ (206 mg, 5.44 mmol). The mixture was allowed to warm to 0 °C over 2 h, and then aqueous HCl (2 M, 10 mL), EtOAc (30 mL), and brine (20 mL) were added and the organic layer was separated. The aqueous layer was re-extracted with EtOAc (5 × 20 mL), the combined organic phases were dried ($MgSO_4$), and solvents were removed in vacuo to give a colorless oil. Purification by column chromatography (silica gel, MeOH/CH_2Cl_2 0:1 → 3:97) gave the title triols (781 mg, 2.17 mmol, 80%, er ∼ 6:1) as a white solid: mp 49−51 °C; $[\alpha]^{26}_D$ +12.4 ($CHCl_3$, *c* 0.45); IR (neat) 3375, 2922, 2852 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ 4.00 (1H, dt, J = 4.0, 6.3 Hz), 3.83 (1H, dt, J = 4.8, 6.8 Hz), 3.64 (1H, dd, J = 6.0, 11.2 Hz), 3.6 (1H, dd, J = 6.3, 11.2 Hz), 3.56−3.51 (1H, m), 3.46−3.41 (1H, m), 2.04−1.80 (4H, m), 1.55−1.45 (2H, m), 1.42−1.26 (24H, m), 0.93 (3H, t, J = 6.5 Hz); ^{13}C NMR (100 MHz, CD_3OD) δ 83.8, 80.8, 75.2, 74.9, 65.1, 35.2, 33.1, 30.8, 30.7, 30.5, 28.9, 28.6, 26.9, 23.7, 14.4; LRMS (ES^+) *m*/*z* 381 ($[M + Na]^+$).

(*S*)-2-Hydroxy-2-((2*S*,5*R*)-5-((*R*)-1-hydroxypentadecyl)tetrahydrofuran-2-yl)ethyl 4-methylbenzenesulfonate (er ∼ 6:1). To a solution of the above triol (146 mg, 0.41 mmol, er ∼ 6:1) in benzene (5 mL) was added Bu_2SnO (121 mg, 0.49 mmol), and the mixture was heated at reflux for 3 h. After the reaction mixture was cooled to rt, TsCl (86 mg, 0.45 mmol) was added followed after 10 min by TBAB (132.17 mg, 0.41 mmol). After 30 min, the reaction mixture was concentrated in vacuo. Purification of the residue by column chromatography (silica gel, EtOAc/hexane 20:80 → 35:65) gave the monotosylate (210 mg, 0.41 mmol, 100%, er ∼ 6:1) as a white solid: mp 70−72 °C; $[\alpha]^{26}_D$ +10.2 ($CHCl_3$, *c* 0.30); IR (neat) 3425, 3309, 2915, 2848, 1593 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.85 (2H, d, J = 8.2 Hz), 7.35 (2H, d, J = 8.2 Hz), 4.09 (2H, d, J = 6.0 Hz), 4.00 (1H, dt, J = 3.0, 6.8 Hz), 3.84 (1H, dt, J = 4.0, 6.9 Hz), 3.77−3.71 (1H, m), 3.45−3.39 (1H, m), 3.36 (1H, br). 2.54 (1H, br), 2.45 (3H, s), 2.02−1.7 (4H, m), 1.47−1.40 (2H, m), 1.34−1.20 (24H, m), 0.88 (3H, t, J = 6.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.0, 132.9, 130.0, 128.1, 82.7, 78.6, 74.2, 71.7, 71.6, 34.6, 32.0, 29.8, 29.7, 29.4, 28.2, 27.9, 25.9, 22.8, 21.7, 14.2; LRMS (ES^+) *m*/*z* 535 ($[M + Na]^+$).

(*R*)-1-((2*R*,5*S*)-5-((*S*)-oxiran-2-yl)-tetrahydrofuran-2-yl)pentadecan-1-ol (10B) (er ∼ 6:1). To a solution of the above tosylate (750 mg, 1.46 mmol) in THF (2 mL) and MeOH (10 mL) at 0 °C was added dried powdered K_2CO_3 (253 mg, 1.83 mmol) in one batch. The solution was allowed to stir at rt for 1 h before concentration in vacuo to give an oily residue which was filtered through a plug of silica gel, eluting with EtOAc/hexane (3:7). Following removal of the solvents in vacuo, the residue was purified by column chromatography (silica gel, EtOAc/hexane 3:7) to give the epoxides **10A/B** (470 mg, 1.39 mmol, 95%, er ∼ 1:6) as a white solid: mp 36−40 °C; $[\alpha]^{26}_D$ +16.6 ($CHCl_3$, *c* 0.25); IR ν_{max} (neat) 3420, 2921, 2825, 1462 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.06 (1H, dt, J = 3.2, 6.9 Hz), 3.88 (1H, dt, J = 4.5, 7.4 Hz), 3.47−3.30 (1H, m), 3.03 (1H, td, J = 3.0, 4.0 Hz), 2.84−2.72 (2H, m), 2.80 (1H, br), 2.17−1.83 (4H, m), 1.57−1.12 (26 H, m), 0.88 (3H, t, J = 6.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 83.1, 77.2, 74.3, 54.6, 44.4, 34.8, 32.0, 29.9, 29.8, 29.5, 29.3, 28.2, 26.0, 22.8, 14.2; LRMS (ES^+) *m*/*z* 363 ($[M + Na]^+$); HRMS (ES) $C_{21}H_{40}O_3Na^+$ calcd 363.2870, found 363.2867.

(*S*)-1-((2*S*,5*R*)-5-((*R*)-1-Hydroxypentadecyl)tetrahydrofuran-2-yl)tridec-12-en-1-ol (11B) (er ∼ 6:1). At −60 °C, undec-10-enylmagnesium bromide in THF (2 mL of a 0.4 M solution, 0.8 mmol) was added dropwise to a suspension of CuBr (70 mg, 0.367 mmol) in THF (5 mL). The mixture was warmed to −30 °C (gray color) and after 20 min recooled to −60 °C whereupon a solution of epoxide **10A/B** (50 mg, 0.147 mmol, er ∼ 1:6) in THF (5 mL) was added dropwise. The mixture was allowed to warm to −20 °C over 1 h. Aqueous NH_4Cl/NH_3 (9:1, 12 mL) was added to the reaction mixture, followed by EtOAc (20 mL). The organic phase was separated, and the aqueous phase was re-extracted with EtOAc (2 × 20 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo to give a yellow oil. Purification by column chromatography (silica gel, EtOAc/hexane 7:93 → 1:4) gave the title olefin (73 mg, 0.16 mmol, 82%) as a white solid: mp 48−51 °C; $[\alpha]^{27}_D$ +0.5 ($CHCl_3$, *c* 0.7); IR (neat) 3431, 2918, 2849 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.82 (1H, tdd, J = 7.0, 10.1, 17.0 Hz), 4.99 (1H, tdd, J = 1.4, 2.3, 17.0 Hz), 4.93 (1H, tdd, J = 1.2, 2.3, 10.1 Hz), 3.86−3.79 (2H, m), 3.42 (2H, td, J = 5.3, 6.7 Hz), 2.37 (2H, br), 2.04 (2H, q, J = 7.0 Hz), 1.99−1.86 (2H, m), 1.81−1.69 (2H, m) 1.56−1.18 (42H, m), 0.88 (3H, t, J = 6.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.4, 114.2, 82.8, 74.5, 34.3, 33.9, 32.1, 29.8, 29.7, 29.6, 29.5, 29.3, 29.1, 28.3, 25.8, 22.8, 14.2; LRMS (ES^+) *m*/*z* 517 ($[M + Na]^+$); HRMS (ES) $C_{32}H_{62}O_3Na^+$ calcd 517.4591, found 517.4581.

(4*E*)-4,5-Didehydro-*cis*-uvariamicin I (15B) (dr ∼ 6:1). The procedure was carried out by an adaptation of the method described by Trost and Toste.[9] Under an atmosphere of nitrogen, $[CpRu(CH_3CN)_3]^+PF_6^-$ (17.4 mg, 0.04 mmol, 5 mol %) was added to a stirred solution of the terminal olefin **11B** (200 mg, 0.4 mmol, er ∼ 6:1) and alkyne **13** (120 mg, 0.48 mmol) in DMF (15 mL). The solution was allowed to stir at rt for 1 h before the reaction mixture was passed through a plug of silica (4 cm, EtOAc/hexane, 2:3) and then concentrated in vacuo. Purification by column chromatography (silica gel,

EtOAc/hexane 1:9 → 1:1) gave the title butenolide **15B** (166 mg, 0.29 mmol, 70%) as a white solid and uncyclized nitrobenzyl ester (21 mg, 0.028 mmol, 7%) as a white solid. Data for the title compound **15B**: mp 65−68 °C; $[\alpha]^{27}_{D}$ +10.6 ($CHCl_3$, *c* 0.39); IR (neat) 3428, 2917, 2848, 1739, 1470 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.99 (1H, q, J = 1.5 Hz), 5.58 (1H, ttd, J = 1.2, 6.8, 15.0 Hz), 5.47 (1H, ttd, J = 1.2, 6.5, 15.0 Hz), 5.03 (1H, qq, J = 1.7, 6.8 Hz), 3.865−3.79 (2H, m), 3.45−3.40 (2H, m), 2.98−2.94 (2H, m), 2.36 (2H, br), 2.06−1.99 (2H, m), 1.98−1.89 (2H, m), 1.81−1.71 (2H, m), 1.54−1.20 (40H, m), 1.42 (3H, d, J = 6.8 Hz), 0.89 (3H, t, J = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.6, 149.5, 134.3, 133.7, 124.3, 82.8, 77.7, 74.4 34.2, 32.6, 32.0, 29.8, 29.7, 29.7, 29.6, 29.5, 29.4, 29.2, 28.5, 28.2, 25.8, 22.8, 19.2, 14.2; LRMS (ES^+) m/z 613 ($[M + Na]^+$), 591 ($[M + H]^+$); HRMS (ES) $C_{37}H_{66}O_5Na^+$ calcd 613.4802, found 613.4795.

***cis*-Uvariamicin I (3A/B, dr ∼ 1:6).** To a solution of 4, 5-dihydro-*cis*-uvariamicin I B (**15B**, 160 mg, 0.27 mmol, dr ∼ 6:1) and $TsNHNH_2$ (503 mg, 2.7 mmol) in THF (5 mL) was added a solution of NaOAc (81.4 mg, 2.7 mmol) in H_2O (2 mL). The mixture was heated at 80 °C for 36 h. EtOAc (10 mL) and brine (3 mL) were added. The organic phase was separated, and the aqueous phase was extracted with EtOAc (2 × 10 mL). The combined organic extracts were dried ($MgSO_4$), and solvents were removed in vacuo to give a white solid. The residue was dissolved in Et_2O, washed with 1 M HCl solution, brine, saturated $KHCO_3$, and then dried ($MgSO_4$). Purification by column chromatography (silica gel, EtOAc/hexane 15:85 → 25:75) gave *cis*-uvariamicin I (**3A/B**) (144 mg, 0.24 mmol, 90%, dr ∼ 1:6) as a white solid. Spectroscopic data are consistent with those reported for a mixture of **3** and **5**:[7] mp 68−72 °C; $[\alpha]^{27}_{D}$ +12.5 ($CHCl_3$, *c* 0.87); IR (neat) 3513, 3437, 2915, 2847, 1743, 1469, 1373, 1169, 1120, 1078 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.98 (1H, q, J = 1.6 Hz), 4.99 (1H, qq, J = 1.6, 6.8 Hz), 3.85−3.78 (2H, m), 3.42 (2H, td, J = 5.3, 6.6 Hz), 2.55 (2H, br, s), 2.28−2.23 (2H, m), 1.98−1.88 (2H, m), 1.79−1.69 (2H, m), 1.62−1.10 (46H, m), 1.47 (3H, d, J = 6.8 Hz,), 0.87 (3H, t, J = 6.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.0, 148.9, 134.5, 82.8, 77.5, 74.5, 34.2, 32.0, 29.8, 29.7, 29.6, 29.4, 29.4, 29.3, 28.2, 27.5, 25.9, 25.3, 22.8, 19.3, 14.2; LRMS (ES^+) m/z 615 ($[M + Na]^+$), 593 ($[M + H]^+$); HRMS (ES^+) $C_{37}H_{68}O_5^+$ calcd 592.496, found 592.494.

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Supporting Information Available: Experimental procedures and spectroscopic characterization data for *cis*-reticulatacin series **6**−**8** and **13**. Spectroscopic characterization data for **9A** and **14**. Copies of ^1H and ^{13}C NMR spectra for compounds **3**, **5**, **7**−**11**, and **13**−**15** and *cis*-reticulatacin series. HPLC chromatograms. This material is available free of charge via the Internet at http://pubs.acs.org.