Synthesis of the fatty acid of pramanicin

Christopher Cow, David Valentini, and Paul Harrison

Abstract: The natural product tetradec-2-enoic acid-4,5-epoxide (**2**), which is also a component of the antibiotic pramanicin (**1**), was prepared in racemic form by a glycoluril-template directed approach. Two sequential additions of acetate units to decanoic acid are effected by intramolecular condensations on the template, mimicking the proposed biosynthetic pathway to **1**. Cleavage of the grown *trans,trans*-tetradeca-2,4-dienoyl chain from the template and epoxidation yields **2**. The reaction sequence illustrates the applicability of this biomimetic approach to total synthesis of natural products.

Key words: pramanicin, biomimetic, glycoluril, template.

Résumé : On a préparé la forme racémique de l'acide 4,5-époxy tétradéc-2-énoïque (**2**), un produit naturel qui est également un constituant de l'antibiotique pramanicine (**1**), en utilisant l'approche directe à l'aide d'un modèle glycolurile. On a effectué deux additions séquentielles d'unités acétates sur l'acide décanoïque par condensations intramoléculaires sur le composé modèle, imitant ainsi la voie biosynthétique proposée pour le composé **1**. Le clivage de la chaîne *trans-trans*-tétradéca-2,4-diénoyle en formation à partir du composé modèle et son époxydation subséquente conduisent au composé **2**. La séquence des réactions illustre la validité de cette approche biomimétique lors de la synthèse totale des produits naturels.

Mots clés : pramanicine, biomimétique, glycolurile, modèle.

[Traduit par la rédaction]

Introduction

Pramanicin (**1**) and the related fatty acid **2** (Scheme 1) are co-occurring natural products isolated recently by Schwartz et al. from an unidentified fungus in grass (1). The antibiotic activity of **1** against the fungal pathogen *Cryptococcus neoformans* (1), the causative agent of meningitis in AIDS patients, makes it an interesting target for synthesis. Such a synthesis should allow for the determination of the absolute stereochemistry of the epoxide, as well as for the preparation of analogues for structure–activity correlations.

The glycoluril **3** is being developed in our group as a template to effect intramolecular crossed-Claisen-like condensations between two acyl units (2, 3) in a manner that mimics some of the features of polyketide and fatty acid biosynthesis (4). To utilize this approach in the synthesis of **1**, the fatty acid **2** was chosen as a key intermediate, since a Claisen-like condensation between **2** and an appropriately substituted and protected pyrrolidinone would generate the carbon skeleton of **1** (Scheme 1). Further, **2** could be derived from a series of Claisen-type condensations between acyl units, followed by functional group manipulations. Although the biosynthetic pathway to **1** and **2** has not been investigated, it is probable that this retrosynthetic analysis corresponds to the sequence of events in the biosynthesis of **1**.

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This paper is dedicated to Professor William A. Ayer on the occasion of his 65th birthday.

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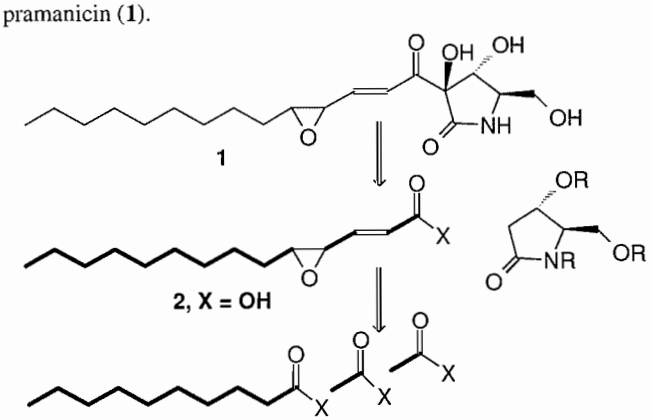
Scheme 1. Retrosynthetic, and probable biogenetic, analysis of pramanicin (**1**).

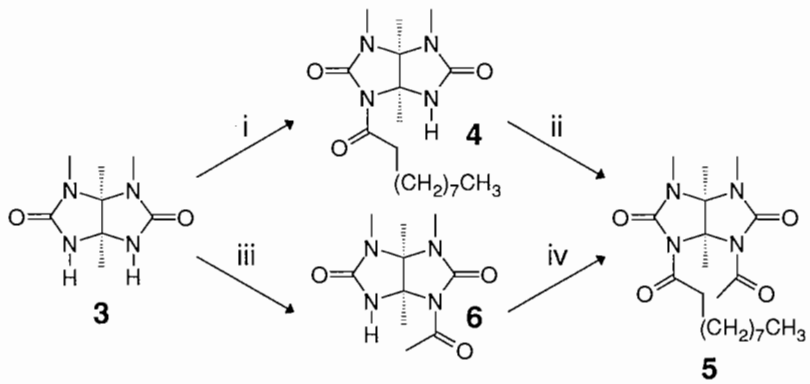


Herein, we describe the application of this methodology to the synthesis of **2** from decanoic acid. Although **2** could in principle be constructed by sequential "head-to-tail" condensations of seven acetate units, we chose to assemble the target from decanoyl chloride, which is the last readily available acid derivative in the proposed synthetic sequence.

Results

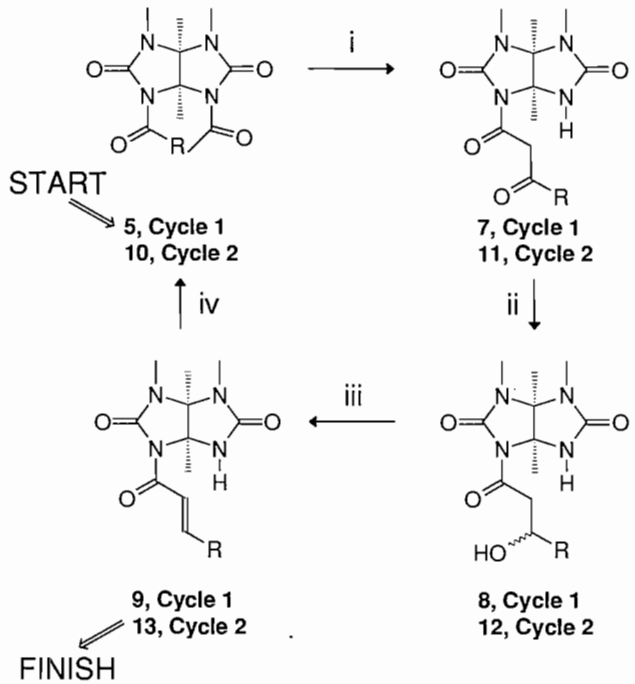
Treatment of glycoluril **3** (5) with *n*-BuLi, then decanoyl chloride, afforded the decanoyl derivative **4** (Scheme 2). As with other acylations of glycoluril **3** (2, 3), only a small amount of didecanoylglycoluril was formed in this reaction; presumably, the steric hindrance provided by the first acyl moiety prevents acylation at the second, free, NH site. Further acylation can be accomplished, however, by treating **4** with *n*-BuLi, then acetyl chloride, to give the decanoyl acetyl derivative **5**. This reaction, which proceeded rather poorly, was not optimized since the yield of **5** was considerably improved by acetylation of

Scheme 2.



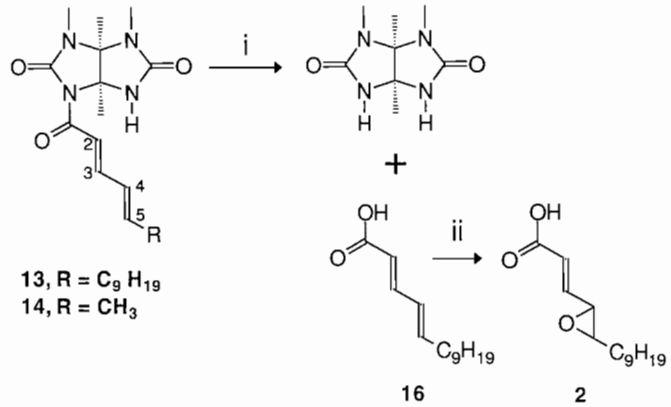
Reagents: (i) *n*-BuLi, THF, reflux, 2 h, then $C_9H_{19}COCl$, r.t., 1 h, 65%; (ii) *n*-BuLi, THF, r.t., 10 min, then CH_3COCl, 1 h, 38%; (iii) $(CH_3CO)_2O$, neat, reflux, 16 h, 78%; (iv) *n*-BuLi, THF, reflux, 2 h, then $C_9H_{19}COCl$, r.t., 1 h, 75%.

Scheme 3.



Reagents: (i) *t*-AmOLi, THF, 0°C, 20 min, then $NaHSO_4$(aq); for **7**: 65%, for **11**: 50%; (ii) $NaBH_4$, MeOH, 0°C, 10 min, then AcOH; for **8**: 79%, for **12**: 24%; (iii) $(CF_3CO)_2O$, 1 h, then excess Et_3N, reflux 20 min; for **9**: 76%, for **13**: 94%; (iv) *n*-BuLi, THF, r.t., 10 min, then CH_3COCl, 1 h, 61%, Cycle 1 to Cycle 2. R = C_9H_{19} for Cycle 1, R = $C_9H_{19}CH{=}CH$ for Cycle 2.

Scheme 4.



Reagents: (i) *t*-BuOK (6 equiv.), H_2O (2 equiv.), Et_2O, r.t., 3 h, 68%; (ii) Oxone, H_2O, PhH, Me_2CO, 18-crown-6, 0°C, pH 7.5, 3 h, 35%.

glycoluril **3** first, to give **6** (2, 3), followed by treatment with *n*-BuLi and decanoyl chloride.

The Claisen-like condensation between the acetyl and decanoyl groups of **5** was effected with lithium *tert*-amylate in THF at 0°C (Scheme 3). As in our previous studies (2, 3), the condensation proceeded rapidly under mild conditions to give **7** as the sole detectable product. Compound **7** was reduced to the β-hydroxydodecanoylglycoluril **8**, from which elimination of water proceeded smoothly to give the unsaturated derivative **9**, which was >99% *trans* by NMR. The sequence of reactions was now repeated: acetylation of **9** gave **10**, and intramolecular Claisen-like condensation afforded ketone **11**. Reduction of **11** yielded alcohol **12**, and elimination of water gave exclusively the *trans,trans* isomer of tetradeca-2,4-dienoylglycoluril (**13**).

It now remained to convert **13** to **2**. It was unclear, however, whether to remove the acyl moiety from the glycoluril template prior to or after the epoxidation of the 4,5 double bond, and we therefore investigated both possible routes using *trans,trans*-hexa-2,4-dienoylglycoluril **14** (3) as a model substrate. Treatment of **14** with *m*CPBA furnished the desired epoxide **15** in good yield and with high selectivity for the 4,5 over the 2,3 double bond. However, when **15** was treated with a variety of reagents that were expected to effect cleavage of the acyl–glycoluril bond (LiOH, LiOMe, LiOBn, or KO*t*Bu–H_2O), in all cases these reactions failed to yield the desired products. In contrast, when either **13** or **14** was treated with potassium *tert*-butoxide–water according to the procedure of

Gassman et al. (6), the free acids were obtained in good yields (Scheme 4). Subsequent epoxidation of tetradeca-2,4-dienoic acid **16** (7, 8) using oxone (9) required the use of a biphasic mixture of benzene, 18-crown-6, aqueous buffered phosphate, and acetone in order to solubilize the components. This reaction is again highly selective for the 4,5 double bond, affording racemic epoxide **2**, which was spectroscopically identical to the natural product.

Discussion

This sequence of reactions presumably corresponds to the events occurring on the putative polyketide synthase that is responsible for formation of **2** in vivo. After assembly of the decanoyl chain from five acetate units in the conventional manner of fatty acid biosynthesis, the condensing subunit of the enzyme is loaded with the decanoyl moiety, and a malonyl group, which acts as an acetyl enolate equivalent, is then covalently attached. Decarboxylative condensation on the enzyme surface generates a new C—C bond; likewise, covalent attachment of an acetyl group to decanoyl glycoluril **4**, followed by intramolecular Claisen-like condensation, generates a 12-carbon chain. Further, both the β-ketoacyl enzyme and the corresponding glycoluril **7** undergo reductions to β-hydroxyacyl groups, and subsequent eliminations of water. The resulting enoyl derivatives can be reacylated and the sequence repeated, resulting in the iterative growth of long chains on both the enzyme and the mimic. Finally, cleavage of the newly synthesized acyl chain regenerates the glycoluril template or the enzyme, which can in either case be recycled.

Since this methodology parallels the enzymatic events, it should prove useful for the synthesis of natural products, as well as putative precursors for the investigation of biosynthetic pathways. This sequence represents the first application of this methodology to the synthesis of a natural product that is not readily available, and illustrates the potential of the approach for the synthesis of a variety of fatty acid and polyketide natural products, or analogues thereof. The approach provides a useful method for effecting Claisen condensations on α,β-unsaturated acyl groups; no detectable conjugate addition was observed in these cases, presumably due to the orientational effects of the glycoluril template. The preparation of the pyrrolidinone moiety and condensation with **2** to give pramanicin will be described in due course.

Experimental

General

All reactions were performed in flame-dried glassware, under a positive pressure of dry nitrogen, unless otherwise noted. Air- and moisture-sensitive compounds were transferred by syringe. Melting points are uncorrected. Proton and carbon-13 NMR spectra were obtained on a Bruker AC-200 spectrometer. The reference for NMR chemical shifts was TMS. Data are given as chemical shift (integral, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constant(s) (Hz), assignment). Fourier transform infrared (FTIR) spectra were recorded on a Bio-Rad SPC 3200 spectrophotometer. Mass spectra were recorded on a VG analytical ZAB-E machine using electron impact (EIMS). High-resolution mass spectra were also recorded on the same spectrometer. Flash column chromatography was performed with Kieselgel 60 (230–400 mesh ASTM) according to the method of Still et al. (10). THF was freshly distilled under nitrogen protection from potassium–benzophenone. *n*-Butyllithium (*n*-BuLi) was titrated using 2,5-dimethoxybenzyl alcohol in THF (11). Water was obtained from a Millipore purification device.

Preparation of 1-decanoyl-3,4,7,8-tetramethylglycoluril (4)

To a suspension of glycoluril **3** (1 g, 5.1 mmol) in THF (60 mL) at reflux was added *n*-BuLi (3.45 mL of a 1.6 M solution in hexane, 5.5 mmol). The mixture was cooled to room temperature and decanoyl chloride (1.3 mL, 1.2 g, 6.3 mmol) was added. After stirring for 1 h, solid ammonium bicarbonate (2 g) was added. The mixture was filtered, and the residue was washed with chloroform (2 × 30 mL). The filtrate was evaporated, and the product was purified by flash column chromatography in EtOAc to give 1.17 g (3.3 mmol, 65%) of **4** as white crystals. ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 6.09 (1H, br s, N*H*), 2.98 (3H, s, NCH_3), 2.84 (3H, s, NCH_3), 2.81 (2H, m, O=C-CH_2), 1.65 (3H, s, CH_3), 1.56 (2H, pent, J = 7.3 Hz, O=C-CH_2CH_2), 1.52 (3H, s, CH_3), 1.24 (12 H, br s, CH_2), 0.83 (3H, t, J = 6.6 Hz, CH_2CH_3); ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 174.28 (*C*=O), 157.20 (NN*C*=O), 152.94 (NN*C*=O), 78.53 (*C*NN), 77.63 (*C*NN), 36.36, 31.78, 29.33, 29.18 (2C), 29.07, 27.00, 26.34, 24.23, 22.58, 19.60, 15.67, 14.02; EIMS *m/z*: 352 $[M]^+$, 253, 240 (base), 199, 156, 141, 125; HRMS (EI) calcd. for $C_{18}H_{32}N_4O_3$: 352.2474; found: 352.2482.

1-Decanoyl-6-acetyl-3,4,7,8-tetramethylglycoluril (5)

Method 1

A solution of decanoylglycoluril **4** (500 mg, 1.4 mmol) in THF (30 mL) at 0°C was treated with *n*-BuLi (0.88 mL of a 1.6 M solution in hexane, 1.4 mmol). The mixture was stirred for 10 min, then acetyl chloride (0.12 mL, 0.13 g, 1.7 mmol) was added and stirring continued for 1 h, during which time the mixture warmed slowly to room temperature. Aqueous $NaHSO_4$ (5 mL, 1 M) was added, and the mixture was extracted with chloroform (3 × 30 mL). The chloroform layers were combined, washed with water, dried over Na_2SO_4, and concentrated. Flash column chromatography of the residue in EtOAc gave white crystals of **5** (214 mg, 38%) and unreacted **4** (159 mg, 32%).

Method 2

A solution of acetylglycoluril **6** (524 mg, 2.2 mmol) in THF (50 mL) was treated with *n*-BuLi (1.5 mL of a 1.6 M solution in hexane, 2.4 mmol) at 0°C for 30 min. Decanoyl chloride (0.54 mL, 0.50 g, 2.6 mmol) was added and the solution was stirred for 1 h, during which time the mixture warmed slowly to room temperature. Aqueous $NaHSO_4$ (5 mL, 1 M) was added, and the mixture was extracted with chloroform (3 × 30 mL). The chloroform layers were combined, washed with water, dried over Na_2SO_4, and concentrated. Flash column chromatography of the residue in EtOAc gave product **5** (517 mg, 62%) and unreacted **6** (34 mg, 6%). IR (KBr pellet): 2921, 2853 (C-H str.), 1684-1749 (br C=O str.), 1332, 1092, 759, 607; ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 2.92 (6H, s, NCH_3), 2.81 (2H, m, O=CCH_2), 2.44 (3H, s, O=CCH_3), 1.90 (3H, s, CH_3), 1.56 (4H, m, O=CCH_2CH_2 and O=$CH_2CH_2CH_2$),

1.45 (3H, s, CH_3), 1.22 (10 H, br m, CH_2), 0.83 (3H, t, J = 7 Hz, CH_2CH_3); ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 173.73 (*C*=O), 170.50 (*C*=O), 153.06 (2 NN*C*=O), 80.48 (*C*NN), 77.63 (*C*NN), 37.61, 31.80, 29.37–29.05 (5 C overlapping), 26.70, 26.14, 24.31, 22.60, 19.06, 14.51, 14.04; EIMS *m/z*: 394 $[M]^+$, 353, 295, 282, 253, 241 (base), 199, 168, 141, 125.

1-(3′-Oxododecanoyl)-3,4,7,8-tetramethylglycoluril (7)

Acetyl decanoyl glycoluril **5** (4.7 g, 12 mmol) was dissolved in THF (200 mL). Separately, *n*-BuLi (9.4 mL of a 1.6 M solution in hexane, 15 mmol) was added to *tert*-amyl alcohol (2.6 mL, 24 mmol) in THF (10 mL) at 0°C, and the mixture was stirred for 10 min. The amylate solution was cannulated into the glycoluril solution at 0°C, and the mixture was stirred for 2 h at 0°C. Aqueous $NaHSO_4$ (20 mL, 1 M) was added, and the mixture was extracted into chloroform. The chloroform layers were combined, washed with water, dried over Na_2SO_4, and concentrated. Flash column chromatography of the residue in EtOAc gave **7** (3.0 g, 65%) as white crystals and unreacted **5** (0.92 g, 17%). IR (KBr pellet): 3337 (N-H str.), 2925, 2854 (C-H str.), 1724 (br C=O str.), 1411, 1111, 760; ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 6.05 (1H, s, N*H*), 4.29 (1H, d, J = 16.3 Hz, O=C-CH_aH-C=O), 3.52 (1H, d, J = 16.3 Hz, O=C-CHH_b-C=O), 2.93 (3H, s, NCH_3), 2.83 (3H, s, NCH_3), 2.48 (2H, m, O=CCH_2CH$_2$), 1.71 (3H, s, CH_3), 1.65 (2H, m, O=CCH$_2$CH_2),1.53 (3H, s, CH_3), 1.22 (12 H, br m, CH_2), 0.84 (3H, t, J = 6.0 Hz, CH_3); ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 203.66 (*C*=O), 167.42 (*C*=O), 157.14 (*C*=O), 152.73 (*C*=O), 76.71, 76.60, 51.48, 42.06, 31.80, 29.34 (2C), 29.20, 28.99, 27.06, 26.40, 23.28, 22.60, 19.23, 15.68, 14.04; EIMS *m/z*: 394 $[M]^+$ 352, 295, 282, 253, 240, 199, 183, 138, 125 (base); HRMS (EI) calcd. for $C_{20}H_{34}N_4O_4$: 394.2851; found: 394.2589.

1-(3′-Hydroxydodecanoyl)-3,4,7,8-tetramethylglycoluril (8)

Oxododecanoyl glycoluril **7** (45 mg, 0.11 mmol) was dissolved in MeOH (7 mL) at 0°C. $NaBH_4$ (5 mg, 0.16 mmol) was added and the mixture was stirred for 10 min. Glacial acetic acid (1 mL) was added, then solvents were removed on the rotary evaporator. Flash column chromatography of the residue in EtOAc gave **8** (36 mg, 79%) as a white crystalline solid. ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 6.04 (1H, br m, N*H*), 4.00 (1H, m, C*H*OH), 3.21 (1H, dd, J = 17.0, 2.6 Hz, O=C-CH_aH$_b$), 2.98 (3H, s, NCH$_3$), 2.84 (3H, s, NCH$_3$), 2.84 (1H, m, O=CCH_bH$_a$), 1.67 (3H, s, CH_3), 1.60 (3H, s, CH_3), 1.44 (2H, m, HOCHCH_2), 1.23 (15 H, br s, CH_2 and O*H*), 0.85 (3H, t, J = 6.0 Hz, CH_3); ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 167.42 (*C*=O), 157.14 (*C*=O), 152.73 (*C*=O), 77.63, 76.50, 67.95, 43.34, 31.86, 29.55–29.28 (6C), 27.13, 26.41, 22.60, 19.23, 15.68, 14.04; EIMS *m/z*: 396 $[M]^+$ 378, 269, 240, 199, 156, 138, 125 (base).

1-(*trans*-Dodec-2′-enoyl)-3,4,7,8-tetramethylglycoluril (9)

Compound **8** (720 mg, 1.8 mmol) was dissolved in CH_2Cl_2 (10 mL), then trifluoroacetic anhydride (0.77 mL, 5.4 mmol) was added and the mixture was stirred for 1 h. Triethylamine (0.33 mL, 3.6 mmol) in CH_2Cl_2 (5 mL) was added dropwise. After 10 min, further Et_3N (2 mL) was added and the mixture was heated at reflux for 20 min. Evaporation and flash column chromatography of the residue in EtOAc gave **9** (520 mg, 76%) as a white crystalline solid. IR (KBr pellet): 3337 (N-H str.) 2925, 2854 (C-H str.), 1702–1736 (br C=O str.), 1630 (C=C str.), 1468, 1089, 761; ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 7.28 (1H, dd, J = 15.3, 3.2 Hz, O=CC*H*=CH), 7.09 (1H, dt, J = 15.3, 6.6 Hz, O=C-CH=C*H*), 6.09 (1H, s, N*H*), 3.04 (3H, s, NCH_3), 2.89 (3H, s, NCH_3), 2.27 (2H, dt, J = 6.9, 6.9 Hz, O=CCH=CHCH_2), 1.74 (3H, s, CH_3), 1.59 (3H, s, CH_3), 1.49 (2H, m, CH=CHCH$_2$-CH_2), 1.29 (12H, br s, CH_2), 0.90 (3H, t, J = 6.7 Hz, CH_3); ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 165.90 (*C*=O), 157.25 (*C*=O), 153.02 (*C*=O), 150.60 (*C*=O), 121.74, 78.54, 76.68, 32.60, 31.80, 29.40–29.17 (4C), 28.07, 27.06, 26.33, 22.60, 19.70, 15.71, 14.05; EIMS *m/z*: 378 $[M]^+$, 251, 199, 125 (base). HRMS (EI) calcd. for $C_{20}H_{34}N_4O_3$: 378.2632; found: 378.2618.

1-(*trans*-Dodec-2-enoyl)-6-acetyl-3,4,7,8-tetramethylglycoluril (10)

Dodecenoylglycoluril **9** (416 mg, 1.1 mmol) was dissolved in THF (10 mL). *n*-BuLi (0.73 mL of a 1.6 M solution in hexane, 1.1 mmol) was added at 0°C, the mixture was stirred (10 min), and acetyl chloride (86 μL, 1.2 mmol) was added. After 1 h, aqueous $NaHSO_4$ (1 mL, 1 M) was added, and the mixture was extracted with chloroform (3 × 10 mL). The chloroform layers were combined, washed with water (2 × 10 mL), dried over Na_2SO_4, and concentrated. Flash column chromatography in EtOAc afforded **10** as a white solid (282 mg, 61%) and recovered **9** (98 mg, 24%). ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 6.8–7.1 (2H, m, C*H*=C*H*), 2.90 (3H, s, NCH_3), 2.89 (3H, s, NCH_3), 2.39 (3H, s, O=CCH_3), 2.14 (2H, dt, J = 6.9, 6.9 Hz, O=CCH=CHCH_2), 1.89 (3H, s, CH_3), 1.44 (3H, s, CH_3), 1.44 (2H, m, CH=CHCH$_2$CH_2), 1.17 (12H, br s, CH_2), 0.79 (3H, t, J = 6.7 Hz, CH_3); EIMS *m/z*: 420 $[M]^+$, 336, 293, 282, 241, 225, 199, 168, 125 (base).

1-(3′-Oxo-*trans*-tetradec-4′-enoyl)-3,4,7,8-tetramethylglycoluril (11)

Acetyl dodecenoyl glycoluril **10** (395 mg, 0.94 mmol) was dissolved in THF (20 mL). Separately, *n*-BuLi (0.69 mL of a 1.6 M solution in hexane, 1.1 mmol) was added to *tert*-amyl alcohol (0.21 mL, 2.2 mmol) in 5 mL THF and the mixture was stirred for 10 min at 0°C. The *tert*-amylate solution was cannulated into the glycoluril solution, and the mixture was stirred at 0°C for 2 h. Aqueous $NaHSO_4$ (2 mL, 1 M) was added and the mixture was extracted into chloroform (3 × 20 mL). The chloroform layers were combined, washed with water, dried over Na_2SO_4, and concentrated. Flash column chromatography of the residue in EtOAc gave **11** (197 mg, 50%) as a white crystalline solid, and recovered **10** (140 mg, 35%). IR (KBr pellet): 3237 (N-H str.), 2914, 2851 (C-H str.), 1690–1722 (br C=O str.), 1466, 1412, 1090, 759; ^{1}H NMR ($CDCl_3$, 200 MHz), keto form, δ: 7.03 (1H, m, O=C-C*H*=CH), 6.26 (1H, s, N*H*), 6.05 (1H, d, J = 15.8 Hz, O=CCH=C*H*), 4.46 (1H, d, J = 16.2 Hz, O=C-C*H*H-C=O), 3.69 (1H, d, J = 16.2 Hz, O=C-CH*H*-C=O), 2.97 (3H, s, NCH_3), 2.82 (3H, s, NCH_3), 2.17 (2H, m, O=CCH=CHCH_2), 1.72 (3H, s, CH_3), 1.52 (3H, s, CH_3), 1.42 (2H, br m, CH=CHCH$_2$CH_2), 1.22 (12H, br m, CH_2), 0.84 (3H, t, CH_3); enol form, δ: 13.17 (1H, s, O*H*), 6.72 (1H, m, HOC-C*H*=CH), 6.47 (1H, s, O=C-C*H*=COH), 6.20 (1H s, N*H*), 5.84 (1H, dd, J = 12.3, 1.6 Hz, HOC-CH=C*H*), 2.92 (3H, s, NCH_3), 2.82 (3H, s, NCH_3), 2.17 (2H, m, O=C-

CH═CH-CH_2), 1.69 (3H, s, CH_3), 1.52 (3H, s, CH_3), 1.42 (2H, br m, CH═CH-CH$_2$-CH_2), 1.22 (12H, br m, CH_2), 0.84 (3H, t, J = 7.0 Hz, CH_3); ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 193.23, 172.67, 171.29, 170.01, 167.76, 165.84, 157.34, 152.70, 151.19, 150.60, 149.30, 129.36, 125.01, 121.70, 120.81, 90.90, 78.69, 78.52, 76.70, 76.35, 48.93, 32.57, 32.45, 32.18, 31.78, 29.39, 29.30, 29.20, 28.31, 28.02, 27.84, 27.04, 26.37, 22.58, 19.97, 19.67, 19.23, 15.67, 14.02; EIMS *m/z*: 420 [M]$^+$ 378, 240, 141, 125 (base); HRMS (EI) calcd. for $C_{22}H_{36}N_4O_4$: 420.2737; found: 420.2732.

1-(3′-Hydroxy-*trans*-tetradec-4′-enoyl)-3,4,7,8-tetramethylglycoluril (12)

Oxotetradecenoyl glycoluril **11** (84 mg, 0.20 mmol) was dissolved in MeOH at 0°C. $NaBH_4$ (11.3 mg, 0.30 mmol) was added and the mixture was stirred for 10 min. Excess glacial acetic acid (0.5 mL) was added, and solvents were removed on the rotary evaporator. Flash column chromatography of the residue in EtOAc gave **17** (20 mg, 24%). ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 6.04 (1H, s, N*H*), 5.70 (1H, td, J = 6.5, 15.5 Hz, HOCH-CH═C*H*), 5.47 (1H, dd, J = 15.5, 5.0 Hz, HOCH-C*H*═CH), 4.51 (1H, m, C*H*OH), 3.23 (1H, m, OCCH_aH$_b$), 3.01 (1H, m, O═CCH$_b$H$_a$), 2.98 (3H, s, NCH_3), 2.84 (3H, s, NCH_3), 1.96 (2H, m, CH═CH-CH_2), 1.70 (3H, s, CH_3), 1.54 (3H, s, CH_3), 1.23 (15H, br s, CH_2 and O*H*), 0.85 (3H, t, J = 6.7 Hz, CH_3); EIMS *m/z*: 422 [M]$^+$ 406, 348, 295, 282, 240, 206, 199, 125 (base); HRMS (EI) calcd. for $C_{22}H_{38}N_4O_4$: 422.2893; found: 422.2889.

1-(*trans*, *trans*-Tetradeca-2′,4′-dienoyl)-3,4,7,8-tetramethylglycoluril (13)

Alcohol **12** (5.5 mg, 0.013 mmol) was dissolved in CH_2Cl_2 (2 mL), and trifluoroacetic anhydride (5.5 μL, 0.039 mmol) was added. The mixture was stirred for 1 h, then Et_3N (1.8 μL, 0.026 mmol) dissolved in CH_2Cl_2 (1 mL) was added dropwise. After 10 min, an additional 0.5 mL Et_3N was added and the mixture was heated at reflux for 20 min. Evaporation followed by flash column chromatography of the residue in EtOAc afforded **13** (4.9 mg, 94%) as a white crystalline solid. ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 7.40 (1H, dd, J = 15.3, 9.2 Hz, O═CCH═C*H*), 7.22 (1H, d, J = 15.2 Hz, O═C-C*H*), 6.20 (2H, m, C*H*═C*H*CH$_2$), 6.09 (1H, s, N*H*), 3.02 (3H, s, NCH_3), 2.86 (3H, s, NCH_3), 2.17 (2H, q, J = 6.6 Hz, CH═CHCH_2), 1.71 (3H, s, CH_3), 1.56 (3H, s, CH_3), 1.37 (2H, br m, CH═CHCH$_2$CH_2), 1.26 (12H, br m, CH_2), 0.87 (3H, t, J = 6.8 Hz, CH_3); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 166.22 (CH*C*═O), 157.29 (*C*═O), 153.02 (*C*═O), 145.90 (*C*═C), 145.78 (C═*C*), 128.97 (*C*═C), 119.73 (C═*C*), 78.53, 33.00, 31.81, 29.44, 29.36, 29.22, 29.10, 28.60, 27.04, 26.36, 22.59, 19.76, 16.94, 15.71, 14.02; EIMS *m/z*: 404 [M]$^+$, 277, 236, 220, 206, 199, 153, 125 (base), 94, 84, 56, 49; HRMS (EI) calcd. for $C_{22}H_{36}N_4O_3$: 404.2789; found: 404.2795.

***trans*, *trans*-Tetradeca-2,4-dienoic acid (16)**

The tetradecadienoyl adduct **13** (22.7 mg, 0.056 mmol) was added to a slurry of H_2O (2.1 μL, 0.11 mmol) and *t*-BuOK (38 mg, 0.33 mmol) in ether (10 mL). The mixture was stirred at room temperature overnight, then 5% HCl (1 mL) was added and the mixture was extracted with chloroform (3 × 10 mL). The combined extracts were washed with water (10 mL) and brine (10 mL), then dried over Na_2SO_4 and filtered. Concentration of the filtrate gave the title acid as a solid white powder (8.9 mg, 71%). IR (KBr pellet): 3423 (O-H str.), 2924, 2854 (C-H str.), 1686 (C═O str.), 1638 (C═C str.), 1617 (C═C str.), 1466, 1307, 1007, 698; ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 7.34 (1H, m, C*H*═CH), 6.20 (2H, m, 2 C*H*═CH), 5.78 (1H, d, J = 15.22 Hz, O═CC*H*═CH), 2.18 (2H, m, CH═CHCH_2), 1.42 (2H, m, CH═CHCH$_2$-CH_2), 1.26 (12 H, m, CH_2), 0.88 (3H, t, J = 6.12 Hz, CH_3); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 171.36 (C═O), 147.49 (C═C), 146.23 (C═C), 128.22 (C═C), 117.94 (C═C), 33.05, 31.87, 29.50, 29.41, 29.28, 29.18, 28.64, 22.66, 14.07; EIMS *m/z*: 225 [MH]$^+$, 224 [M]$^+$, 216, 195, 181, 164, 153, 142, 125, 109, 97, 84, 49, 45 (base), 43; HRMS (EI) calcd. for $C_{14}H_{25}O_2$ (MH$^+$): 225.1856; found: 225.1864.

***trans*, *trans*-Tetradec-2-enoic acid 4,5-epoxide (2)**

Tetradeca-2,4-dienoic acid (**16**) (100 mg, 0.45 mmol) was added to a well-stirred biphasic mixture of benzene (30 mL) and phosphate buffer (15 mL, pH 7.5, 0.5 M) containing acetone (2 mL) and 18-crown-6 (100 mg, 0.38 mmol) as the phase transfer catalyst. A freshly prepared solution of potassium peroxomonosulfate (Oxone) (0.04 M, 20 mL) with $EDTANa_2$ (4×10^{-4} M) was added dropwise over 30 min. at 6–8°C. During addition, the pH was maintained at 7.5 by addition of 0.5 N KOH. The mixture was stirred for 3 h at room temperature, then extracted with benzene (3 × 30 mL) and dried over $MgSO_4$. The combined extracts were concentrated, then purified by flash column chromatography using 30% EtOAc in hexanes as eluant. Evaporation gave a white powder (35%, 37.5 mg) mp 81–81.5°C; IR (KBr pellet): 3420 (O-H str.), 2916, 2851 (C-H str.), 1730 (C═O str.), 1696 (C═C str.), 1308, 857 (epoxide); ^{1}H NMR (CD_3OD, 200 MHz) δ: 6.62 (1H, dd, ^3J = 7.2, 15.7 Hz, O═C-CH═C*H*), 6.11 (1H, d, ^3J = 15.6 Hz, O═C-C*H*═CH), 3.21 (1H, dd, ^3J = 1.6, 7.0 Hz, CH═CH-C*H*-O), 2.90 (1H, dt, ^3J = 5.9, 2.0 Hz, CH═CH-CH-O-C*H*), 1.58 (2H, m, O-CH-CH_2), 1.44 (2H, m, O-CH-CH$_2$-CH_2), 1.29 (12 H, br s, CH$_2$), 0.89 (3H, t, ^3J = 6.7 Hz, CH_3); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 169.89 (C═O), 147.34 (C═C), 122.56 (C═C), 61.72 (C-O-C), 56.13 (C-O-C), 31.90, 31.86, 29.46, 29.33, 29.26, 25.78, 25.65, 22.65, 14.06 (CH$_3$); EIMS *m/z*: 241 [MH]$^+$ (v. weak), 240 [M]$^+$ (v. weak), 195, 84 (base).

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