Stereoselective Synthesis of (–)-Pironetin by an Iterative Prins Cyclisation and Reductive Cleavage Strategy

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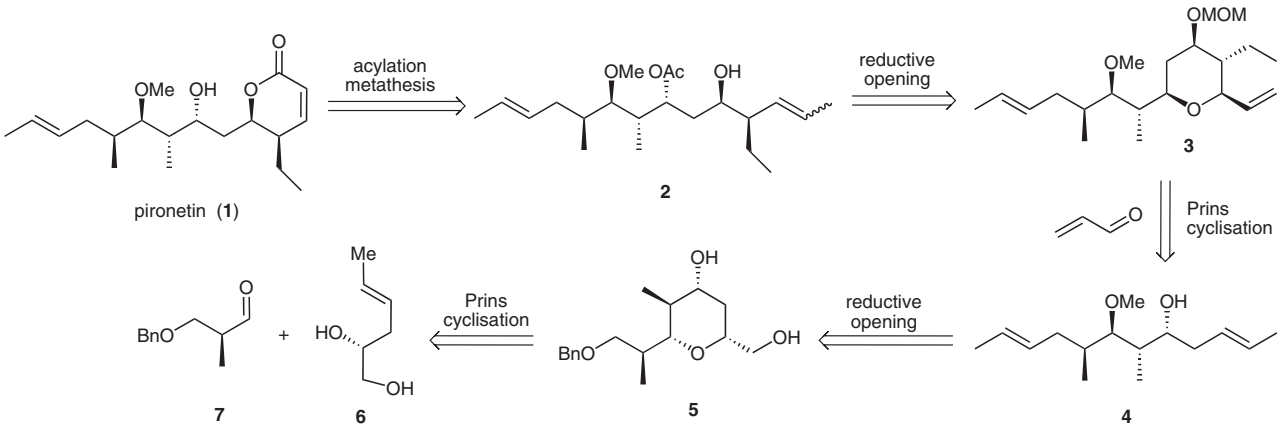
Abstract: A stereoselective synthesis of pironetin, a natural product which is highly immunosuppressive and shows remarkable plant growth regulatory and antitumoral activities, is described. The approach avails successfully the high stereoselection of Prins cyclisation. The route relies, in addition, on the reductive opening of cyclic ethers, olefin metathesis, and lithium acetylide displacement of tosylate.

Key words: natural products, Prins cyclisation, stereoselective synthesis, reductive cleavage, olefin metathesis

Pironetin (**1**) is an unsaturated δ-lactone derivative, which was isolated independently by two research groups from *Streptomyces sp.* NK10958 and from the fermentation broths of *Streptomyces prunicolor* PA-48153, respectively.[1] Apart from plant growth regulatory and immunosuppressive activities, the biological effects of **1** and its derivatives on cell-cycle progression and antitumor activities were reported.[2] More importantly, the mode of action of **1** is different from those established for the immunosuppressant cyclosporine A (CsA) and FK506 that inhibit T cell activation.[3] Pironetin showed suppressive effects on the responses of T and B lymphocytes to mitogens. Inspired by the biological properties and attracted by its consecutive 1,3-*anti*-diol system flanked by 2- or 4-alkyl groups for which we have recently established a method via Prins cyclisation,[4,5] we investigated a synthesis of pironetin. Before the synthetic venture, a careful examination was made on the retrosynthetic analysis (Scheme 1). We first simplified the molecule to the intermediate **2** which has all the required stereochemistry and a homoallylic 1,3-diol system. We envisaged that this intermediate could be easily drawn from pyran **3**, by a reductive opening, which in turn was expected through Prins cyclisation of acrolein and the intermediate **4**. Intermediate **4**, again a homoallylic 1,3-diol system, was envisaged to be available from pyranyl methanol **5** by a reductive opening. Finally, pyranyl methanol **5** could be obtained from Prins cyclisation of known homoallylic alcohol **6** and aldehyde **7**.

Our synthesis of pironetin is outlined in Scheme 2. Prins cyclisation between known homoallylic alcohol **6**[5h] and aldehyde **7**[5e] in the presence of TFA[4a] resulted in the trifluoroacetate derivative of **5** which on direct treatment with K_2CO_3 in MeOH gave tetrahydropyran diol **5**, the only isolable compound in 55% yield. The stereochemical aspects of such Prins cyclisations and structurally very close compounds of **5**have been discussed in detail previously.[4,5] Transformation of the primary hydroxyl group to a tosylate using TsCl and triethylamine and protection of the secondary hydroxyl group as its TBS ether using TBSCl and imidazole resulted in fully protected intermediate **8**. Substitution of the tosylate using NaI in acetone followed by reductive opening[5a] of iodomethylpyran **9** produced alcohol **10**.[6] Alcohol **10** was converted to its methyl ether and the key homologation with homoallyl piv-



Scheme 1

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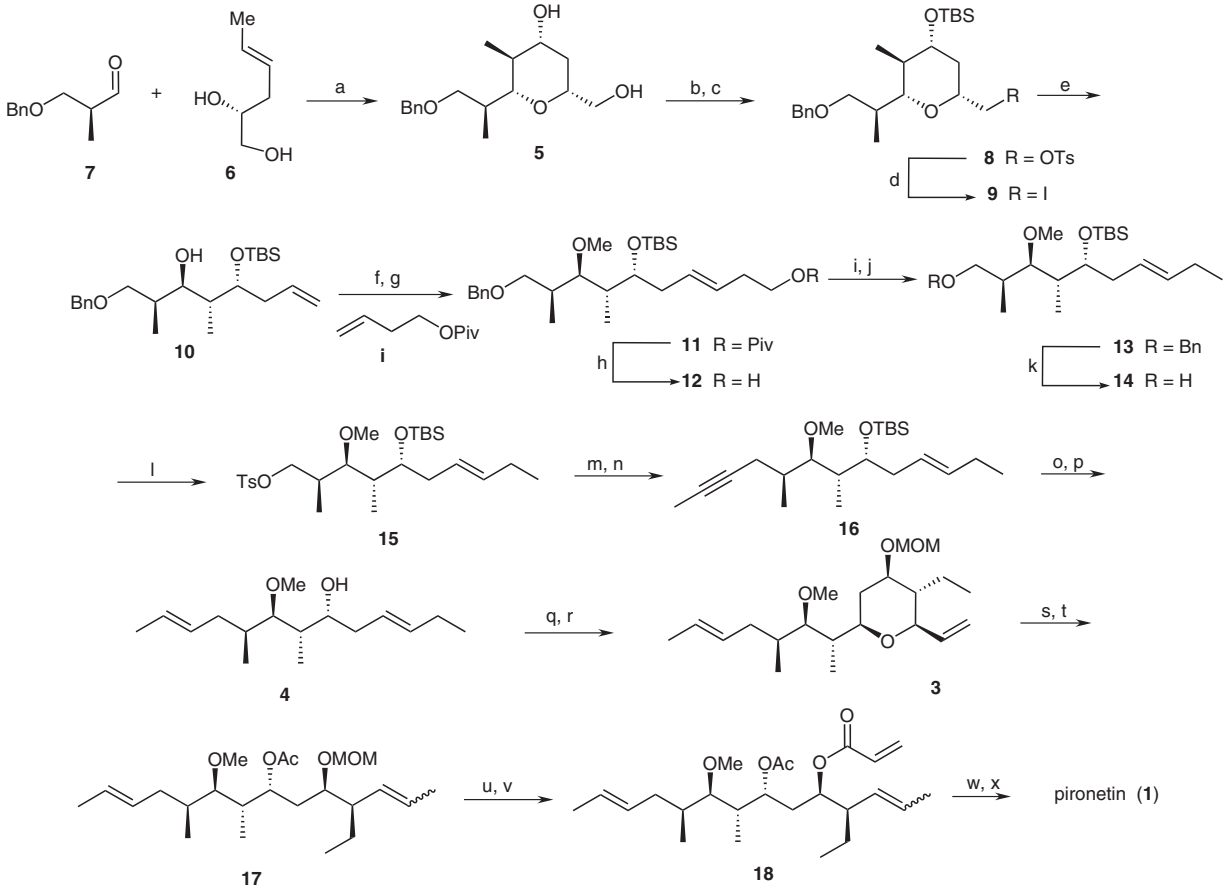

Scheme 2 *Reagents and conditions*: (a) TFA, CH_2Cl_2, 0 °C to r.t., 3 h then K_2CO_3, MeOH, r.t., 30 min, 55%; (b) Et_3N, TsCl, CH_2Cl_2, 0 °C to r.t., 6 h, 95%; (c) TBSCl, imidazole, CH_2Cl_2, 0 °C to r.t., 3 h, 97%; (d) NaI, acetone, reflux, 24 h, 97%; (e) Zn, EtOH, $NaHCO_3$, reflux, 2 h, 80%; (f) NaH, MeI, THF, 0 °C to r.t., 6 h, 98%; (g) i, Grubbs II cat., CH_2Cl_2, 40 °C, 6 h; (h) K_2CO_3, MeOH, r.t., 3 h, 68% (for 2 steps); (i) MsCl, Et_3N, DMAP, CH_2Cl_2, 0 °C to r.t., 30 min; (j) $LiAlH_4$, THF, 0 °C to r.t., 4 h, 95% (for 2 steps); (k) Na, liq NH_3, THF, 10 min, –33 °C, 95%; (l) Et_3N, TsCl, 0 °C to r.t., 6 h, 97%; (m) HC≡CLi·EDA, DMSO, r.t., 2 h, 82%; (n) *n*-BuLi, MeI, THF, –78 °C to r.t., 12 h, 98%; (o) CSA, MeOH, 0 °C to r.t., 15 min, 99%; (p) Na, liq NH_3, THF, –33 °C, 6 h, 90%; (q) acrolein, TFA, CH_2Cl_2, 0 °C to r.t., 3 h then K_2CO_3, MeOH, r.t., 30 min, 58%; (r) MOMCl, DIPEA, CH_2Cl_2, r.t., 3 h, 97%; (s) Na, liq NH_3, THF, –33 °C, 45 min, 94%; (t) Ac_2O, DMAP, CH_2Cl_2, 0 °C to r.t., 2 h, 92%; (u) Me_3SiBr, CH_2Cl_2, –40 °C, 15 min, 76%; (v) acryloyl chloride, Et_3N, DMAP, CH_2Cl_2, 0 °C to r.t., 30 min, 60%; (w) Grubbs II cat., CH_2Cl_2, 50 °C, 8 h, 32%; (x) 3 N HCl, MeOH, 60 °C, 6 h 74%.

alate was achieved using a cross-metathesis protocol[7] to yield **11**. The pivalate group in **11** was removed using K_2CO_3/MeOH, and the resulting alcohol **12** was converted to a mesylate before subjecting it to reductive elimination to yield **13**, suitable for homologation at the other terminus. Thus, deprotection of the benzyl ether using Na/liq NH_3 followed by transformation of the resulting hydroxyl group **14** to tosylate using TsCl and triethylamine produced **15**. Substitution of tosylate with lithium acetylide[8] followed by methylation of the resulting terminal alkyne with MeI/*n*-BuLi in THF yielded homologated **16**. The TBS ether in **16** was cleaved using CSA in MeOH, and the resulting alkynol was subjected to Birch reduction to furnish key homoallylic alcohol **4**.

The stage was now set for a second Prins cyclisation to introduce the remaining stereochemical features. Thus, the second Prins cyclisation was performed on **4** with acrolein, and the resulting pyranol was protected as its MOM ether to yield **3**. Reductive opening[5b] of pyran **3** using Na in ammonia followed by protection of the alcohol as an acetate resulted in **17** as a diastereomeric mixture. The MOM ether in **17** was cleaved using TMSBr,[9] and the resulting alcohol was transformed to its acrylate to produce key fragment **18**. Ring-closing metathesis of **18** in the presence of Grubbs second-generation catalyst,[10a–c,5g] followed by hydrolysis of the acetate group, produced pironetin (**1**) in 53% yield. Of note was the failure of the RCM reaction with Grubbs I[10d] catalyst; this may be attributed to the presence of an internal double bond. Our synthetic material showed spectroscopic and physical data {^{1}H NMR, ^{13}C NMR, IR, R_f and $[\alpha]_D$} consistent with the isolated sample.[1,11]

In summary, we have described a stereoselective approach to pironetin using our recently developed synthetic sequence to access polyketide precursors via Prins cyclisation. This synthetic approach can provide a means for probing the structure–activity relationships of these and other related antifungal agents.

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References and Notes

(1) (a) Kobayashi, S.; Tsuchiya, K.; Harada, T.; Nishide, M.; Kurokawa, T.; Nakagawa, T.; Shimada, N.; Kobayashi, K. *J. Antibiot.* **1994**, *47*, 697. (b) Kobayashi, S.; Tsuchiya, K.; Kurokawa, T.; Nakagawa, T.; Shimada, N.; Iitaka, Y. *J. Antibiot.* **1994**, *47*, 703. (c) Tsuchiya, K.; Kobayashi, S.; Harada, T.; Nishikiori, T.; Nakagawa, T.; Tatsuta, K. *J. Antibiot.* **1997**, *50*, 259.

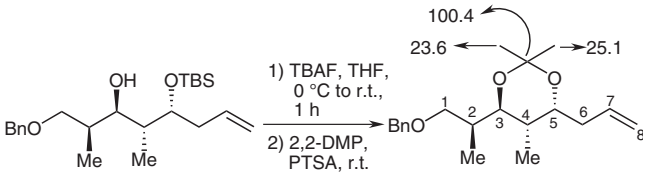
(2) Konodoh, M.; Usui, T.; Kobayashi, S.; Tsuchiya, K.; Nishikawa, K.; Nishikiori, T.; Mayumi, T.; Osada, H. *Cancer Lett.* **1998**, *126*, 29.

(3) For a paper about chemical modifications of pironetin to reduce its toxicity, see: Yasui, K.; Tamura, Y.; Nakatani, T.; Horibe, I.; Kawada, K.; Koizumi, K.; Suzuki, R.; Ohtani, M. *J. Antibiot.* **1996**, *49*, 173.

(4) For examples of the Prins cyclisation, see: (a) Barry, C. S. t. J.; Crosby, S. R.; Harding, J. R.; Hughes, R. A.; King, C. D.; Parker, G. D.; Willis, C. L. *Org. Lett.* **2003**, *5*, 2429. (b) Yang, X.-F.; Mague, J. T.; Li, C.-J. *J. Org. Chem.* **2001**, *66*, 739. (c) Aubele, D. L.; Wan, S.; Floreancig, P. E. *Angew. Chem. Int. Ed.* **2005**, *44*, 3485. (d) Barry, C. S.; Bushby, N.; Harding, J. R.; Willis, C. S. *Org. Lett.* **2005**, *7*, 2683. (e) Cossey, K. N.; Funk, R. L. *J. Am. Chem. Soc.* **2004**, *126*, 12216. (f) Crosby, S. R.; Harding, J. R.; King, C. D.; Parker, G. D.; Willis, C. L. *Org. Lett.* **2002**, *4*, 3407. (g) Marumoto, S.; Jaber, J. J.; Vitale, J. P.; Rychnovsky, S. D. *Org. Lett.* **2002**, *4*, 3919. (h) Kozmin, S. A. *Org. Lett.* **2001**, *3*, 755. (i) Jaber, J. J.; Mitsui, K.; Rychnovsky, S. D. *J. Org. Chem.* **2001**, *66*, 4679. (j) Kopecky, D. J.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **2001**, *123*, 8420. (k) Rychnovsky, S. D.; Thomas, C. R. *Org. Lett.* **2000**, *2*, 1217. (l) Rychnovsky, S. D.; Yang, G.; Hu, Y.; Khire, U. R. *J. Org. Chem.* **1997**, *62*, 3022. (m) Su, Q.; Panek, J. S. *J. Am. Chem. Soc.* **2004**, *126*, 2425. (n) Yadav, J. S.; Reddy, B. V. S.; Sekhar, K. C.; Gunasekar, D. *Synthesis* **2001**, 885. (o) Yadav, J. S.; Reddy, B. V. S.; Reddy, M. S.; Niranjan, N. *J. Mol. Catal. A: Chem.* **2004**, *210*, 99. (p) Yadav, J. S.; Reddy, B. V. S.; Reddy, M. S.; Niranjan, N.; Prasad, A. R. *Eur. J. Org. Chem.* **2003**, 1779.

(5) For our previous applications of Prins cyclisation, see: (a) Yadav, J. S.; Reddy, M. S.; Rao, P. P.; Prasad, A. R. *Tetrahedron Lett.* **2006**, *47*, 4397. (b) Yadav, J. S.; Reddy, M. S.; Prasad, A. R. *Tetrahedron Lett.* **2006**, *47*, 4937. (c) Yadav, J. S.; Reddy, M. S.; Prasad, A. R. *Tetrahedron Lett.* **2005**, *46*, 2133. (d) Yadav, J. S.; Reddy, M. S.; Prasad, A. R. *Tetrahedron Lett.* **2006**, *47*, 4995. (e) Yadav, J. S.; Reddy, M. S.; Rao, P. P.; Prasad, A. R. *Synlett* **2007**, 2049. (f) Yadav, J. S.; Rao, P. P.; Reddy, M. S.; Rao, N. V.; Prasad, A. R. *Tetrahedron Lett.* **2007**, *48*, 1469. (g) Yadav, J. S.; Kumar, N. N.; Reddy, M. S.; Prasad, A. R. *Tetrahedron* **2006**, *63*, 2689. (h) Yadav, J. S.; Kumar Rao, P. P.; Reddy, M. S.; Prasad, A. R. *Tetrahedron Lett.* **2008**, *49*, 5427.

(6) As shown below, compound **10** was subjected to TBS ether cleavage and then transformed to the corresponding acetonide to confirm the *anti* relationship of hydroxyl groups by examination of the ^{13}C NMR spectrum. See: (a) Rychnovsky, S. D.; Skalitzky, D. J. *Tetrahedron Lett.* **1990**, *31*, 945. (b) Evans, D. A.; Rieger, D. L.; Gage, J. R. *Tetrahedron Lett.* **1990**, *39*, 7099; One broad coupling (J = 9.0 Hz) of 3-H of the acetonide in Scheme 3 in its ^1H NMR supported the stereochemistry of the 4-α-methyl group.



Scheme 3

(7) Nicolaou, K. C.; Koftis, T. V.; Vyskocil, S.; Petrovic, G.; Ling, T.; Yamada, Y. M. A.; Tang, W.; Frederick, M. O. *Angew. Chem. Int. Ed.* **2004**, *43*, 4318.

(8) (a) Toshima, K.; Jyojima, T.; Miyamoto, N.; Katohno, M.; Nakata, M.; Mastumura, S. *J. Org. Chem.* **2001**, *66*, 1708. (b) Moune, S.; Niel, G.; Busquet, M.; Eggleston, I.; Jouin, P. *J. Org. Chem.* **1997**, *62*, 3332.

(9) Imoto, H.; Matsumoto, M.; Odaka, H.; Sakamoto, J.; Kimura, H.; Nonaka, M.; Kiyota, Y.; Momose, Y. *Chem. Pharm. Bull.* **2004**, *52*, 120.

(10) (a) Scholl, S.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953. (b) Sanford, M. S.; Love, J. A.; Grubbs, R. H. *J. Am. Chem. Soc.* **2001**, *123*, 6543. (c) Shibahara, S.; Fujino, M.; Tashiro, Y.; Takahashi, K.; Ishihara, J.; Hatakeyama, S. *Org. Lett.* **2008**, *10*, 2139. (d) Schwab, P.; France, M. B.; Ziller, J. W.; Grubbs, R. H. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2039; *Angew. Chem.* **1995**, *107*, 2179.

(11) **Spectroscopic and Physical Data of Selected Compounds**

(2*R*,3*S*,4*R*,6*R*)-2-[(*S*)-1-(Benzyloxy)propan-2-yl]-tetrahydro-6-hydroxymethyl)-3-methyl-2*H*-pyran-4-ol (5)

$[\alpha]_D^{25}$ +18.5 (*c* 1.0, $CHCl_3$); R_f = 0.3 (SiO_2, 60% EtOAc in hexane). IR (neat): 3390, 2926, 2859, 1359, 1158, cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.23–7.30 (m, 5 H), 4.39–4.55 (m, 2 H), 3.21–3.56 (m, 7 H), 2.02–2.11 (m, 1 H), 1.77–1.86 (m, 1 H), 1.22–1.44 (m, 2 H), 0.96 (d, 3 H, J = 6.64 Hz), 0.85 (d, 3 H, J = 6.64 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 138.53, 128.30, 127.48, 79.47, 75.50, 73.33, 73.12, 72.97, 65.83, 40.40, 36.77, 34.10, 12.04, 9.54. ESI-HRMS: *m/z* $[M + Na]^+$ calcd for $C_{17}H_{26}NaO_4$: 317.1728; found: 317.1719.

(2*S*,3*R*,4*R*,5*R*)-1-(Benzyloxy)-5-(*tert*-butyldimethylsilyloxy)-2,4-dimethyloct-7-en-3-ol (10)

$[\alpha]_D^{25}$ +13.9 (*c* 0.65, $CHCl_3$); R_f = 0.6 (SiO_2, 10% EtOAc in hexane). IR (neat): 3500, 2930, 2855, 1461, 1063, 911 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.30–7.27 (m, 5 H), 5.81–5.67 (m, 1 H), 5.08–4.49 (m, 2 H), 4.45–4.56 (m, 2 H), 3.97–3.92 (m, 1 H), 3.75 (d, 1 H, J = 9.82 Hz), 3.53–3.39 (m, 2 H), 2.37–2.20 (m, 2 H), 1.85–1.70 (m, 2 H), 1.46 (br, OH), 0.89–0.87 (m, 12 H), 0.75 (d, 3 H, J = 6.8 Hz), 0.06 (s, 3 H), 0.09 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 138.60, 135.13, 128.24, 127.47, 127.36, 116.90, 116.67, 81.09, 73.86, 72.82, 71.15, 60.70, 40.55, 39.38, 35.30, 26.02, 18.2, 9.7, 9.1, –3.17, –4.37. ESI-HRMS: *m/z* $[M + Na]^+$calcd for $C_{23}H_{40}NaO_3Si$: 415.2644; found: 415.4635.

(3*E*,6*R*,7*S*,8*R*,9*S*,11*E*)-8-Methoxy-7,9-dimethyltridec-3,11-dien-6-ol (4)

$[\alpha]_D^{25}$ +4.0 (*c* 1.3, $CHCl_3$); R_f = 0.5 (SiO_2, 20% EtOAc in hexane); IR (neat): 3420, 2966, 2931, 1715, 1457, 1083, 971 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 5.62–5.29 (m, 4 H), 3.90–3.83 (m, 1 H), 3.48 (s, 3 H), 2.98 (m, 1 H), 2.57 (br, 1 H, OH), 2.27–1.75 (m, 8 H), 1.67 (d, 3 H, J = 6.40 Hz), 0.98 (t, 3 H, J = 7.34 Hz), 0.92 (d, 3 H, J = 7.9 Hz), 0.89 (d, 3 H, J = 7.8 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 134.69, 129.18, 126.58, 125.63, 89.80, 70.6, 61.63, 38.10, 37.8, 37.2, 36.05,

25.63, 17.93, 14.57, 13.8, 10.91. ESI-HRMS: *m/z* [M + Na]$^+$calcd for $C_{16}H_{30}NaO_2$: 277.1987; found: 277.1977.

(2*R*,3*S*,4*R*,6*R*)-3-Ethyl-tetrahydro-6-[(*E*,2*S*,3*R*,4*S*)-3-methoxy-4-methyloct-6-en-2-yl]-2-vinyl-2*H*-pyran-4-ol (3a)

$[\alpha]_D^{25}$ –27.6 (*c* 0.65, $CHCl_3$). IR (neat): 3427, 2967, 2929, 1718, 1457, 1089, 759 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.88–5.71 (m, 1 H), 5.49–5.36 (m, 2 H), 5.26–5.11 (m, 2 H), 3.69–3.45 (m, 3 H), 3.33 (s, 3 H), 3.05 (dd, 1 H, *J* = 9.55, 2.94 Hz), 2.32–2.27 (m, 1 H), 2.08–1.95 (m, 2 H), 1.76–1.41 (m, 7 H), 1.25–1.14 (m, 1 H), 1.02–0.75 (m, 11 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 130.65, 130.44, 128.71, 126.13, 84.8, 80.25, 74.34, 73.43, 70.67, 50.97, 49.21, 40.54, 38.99, 38.25, 35.49, 19.41, 17.96, 11.86, 10.18. ESI-HRMS: *m/z* [M + Na]$^+$ calcd for $C_{19}H_{34}NaO_3$: 333.2405; found: 333.2409.

(4*R*,5*R*,7*R*,8*S*,9*R*,10*S*,12*E*)-4-Ethyl-9-methoxy-5-(methoxymethoxy)-8,10-dimethyltetradeca-2,12-dien-7-yl acetate (17)

IR (neat): 2929, 2855, 1740, 1244, 1097, 966 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.51–5.03 (m, 5 H), 4.63–4.59 (m, 2 H), 3.56–3.41 (m, 1 H), 3.39 (s, 3 H), 3.37 (s, 3 H), 2.84–2.77 (m, 1 H), 2.03 (s, 3 H), 2.17–1.91 (m, 3 H), 1.66 (d, 6 H, *J* = 5.28 Hz), 1.75–1.50 (m, 4 H), 1.45–1.28 (m, 2 H), 0.92–0.79 (m, 9 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.40, 134.51, 132.50, 125.50, 125.5, 96.30, 88.51, 66.99, 68.30, 58.0, 55.62, 49.06, 39.52, 36.42, 35.50, 33.75, 23.65, 21.20, 19.53, 19.35, 15.30, 12.42, 10.25. ESI-HRMS: *m/z* [M + Na]$^+$ calcd for $C_{23}H_{24}NaO_5$: 421.2929; found: 421.2923.

(5*R*,6*R*)-5-Ethyl-5,6-dihydro-6-[(*E*,2*R*,3*S*,4*R*,5*S*)-2-hydroxy-4-methoxy-3,5-dimethylnon-7-enyl]pyran-2-one (1)

$[\alpha]_D^{25}$ –139.5 (*c* 0.35, $CHCl_3$); R_f = 0.3 (SiO_2, 50% EtOAc in hexane); IR (neat): 3479, 2965, 2931, 1718, 1459, 1384, 1088 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.04 (dd, 1 H, *J* = 9.82, 6.04 Hz), 6.04 (d, 1 H, *J* = 9.82 Hz), 5.50–5.32 (m, 2 H), 4.76 (m, 1 H), 4.23 (br d, 1 H), 3.47 (s, 3 H), 3.39 (br, OH), 2.36–2.27 (m, 1 H), 3.00–2.97 (m, 1 H), 2.13–2.06 (m, 1 H), 1.97–1.63 (m, 6 H), 1.67 (d, 3 H, *J* = 5.27 Hz), 1.56–1.45 (m, 1 H), 1.01 (t, 3 H, *J* = 7.18 Hz), 0.97 (d, 3 H, *J* = 7.18 Hz), 0.95 (d, 3 H, *J* = 6.70 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 164.1, 144.8, 121.5, 96.1, 75.2, 69.7, 55.4, 41.8, 29.4, 20.1.164.75, 150.77, 130.08, 126.91, 120.72, 90.2, 77.73, 67.17, 61.55, 39.16, 39.05, 37.32, 36.73, 35.96, 20.76, 17.91, 15.1, 11.88, 10.96. ESI-HRMS: *m/z* [M + Na]$^+$ calcd for $C_{19}H_{32}NaO_4$ 347.2198; found: 347.2205.

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