Enantioselective Syntheses of Monotetrahydrofuran Annonaceous Acetogenins Tonkinecin and Annonacin Starting from Carbohydrates

Tai-Shan Hu, Qian Yu, Yu-Lin Wu,* and Yikang Wu

State Key Laboratory of Bio-organic & Natural Products Chemistry and Shanghai-Hong Kong Joint Laboratory in Chemical Synthesis, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Road, Shanghai 200032, China

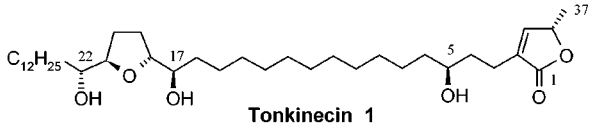
ylwu@pub.sioc.ac.cn

Received September 12, 2000

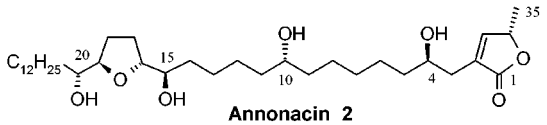
The total synthesis of two mono-THF acetogenins, tonkinecin (**1**) and annonacin (**2**), is reported in full detail. Terminal acetylene **3** prepared from D-glucono-*δ*-lactone and asymmetric dihydroxylation was employed as a common intermediate for both targets **1** and **2**. Pd(0)-catalyzed coupling reaction of **3** with vinyl iodides **4** and **5**, the chiral centers of which were taken from D-xylose and *S*-(−)-ethyl lactate, afforded enyne **26** and **27**, respectively. Selective hydrogenation of **26** or **27** with diimide followed by removal of MOM ethers completed the synthesis of **1**. A coupling reaction between the lithium derivative of **3** and epoxide **6** in the presence of boron trifluoride etherate gave **42**. Both chiral centers in epoxide **6** were taken from L-ascorbic acid. Subsequent catalytic hydrogenation and MOM protection led to **43b**. Introduction of the butenolide moiety by aldol condensation of protected *S*-lactal followed by cleavage of all MOM ethers completed the synthesis of **2**.

Introduction

The Annonaceous acetogenins from the Annonaceae plants have attracted increasing interest[1] because of their potential biological properties, such as cytotoxic, antitumoral, pesticidal, and immunosuppressive activities. Up to now, over 350 acetogenins have been isolated[1a] from 37 species of Annonaceae. The majority of these compounds can be classified into four subgroups according to the number and arrangement of the tetrahydrofuran rings within the molecule: the mono-THF, the adjacent bis-THF, the nonadjacent bis-THF, and the non-THF acetogenins. We have synthesized[1i−l,2] some mono-THF acetogenins by convergent approaches and determined the absolute configuration and activities of 10-isomers of corossolin.[1j] We have also synthesized several structurally simplified acetogenin analogues with potential biological activities have been.[3] Herein, we report the total syntheses of other two mono-THF acetogenins, tokinecin and annonacin, via a carbohydrate-based[1i,l] approach.



Tonkinecin 1



Annonacin 2

Tonkinecin, **1**, which was recently isolated[4] from the roots of *Uvaria tonkinesis* (Annonaceae), is a C-37 mono-THF acetogenin with a C5 carbinol center (to the best of our knowledge only six mono-THF acetogenins with C5 secondary hydroxyl[5] have been known). Annonacin, **2**, the first and most typical mono-THF acetogenin, was isolated[6] from the stem bark of *Annona densicoma* in 1987. The differences between structures of **1** and **2** lie in the

(1) For recent comprehensive reviews, see: (a) Alali, F. Q.; Liu, X.-X.; McLaughlin, J. L. *J. Nat. Prod.* **1999**, *62*, 504. (b) Zafra-Polo, M. C.; Figadere, B.; Gallardo, T.; Tormo, J. R.; Cortes, D. *Phytochemistry* **1998**, *48*, 1087. (c) Casiraghi, G.; Zanardi, F.; Battistini, L.; Rassu, G.; Appendino, G. *Chemtracts Org. Chem.* **1998**, *11*, 803. (d) Cave, A.; Figadere, B.; Laurens, A.; Cortes, D. In *Progress in the Chemistry of Organic Natural Products*; Herz, W., Kirby, G.-W., Moor, R. E., Steglich, W., Tamm, Ch., Eds.; Springer: New York, 1997; Vol. 70, pp 81−288 and references therein. For recent total synthesis, see: (e) Hoppen, S.; Baurle, S.; Koert, U. *Chem. Eur. J.* **2000**, *6*, 2382. (f) Emde, U.; Koert, U. *Eur. J. Org. Chem.* **2000**, 1889. (g) Baurle, S.; Peters, U.; Friedrich, T.; Koert, U. *Eur. J. Org. Chem.* **2000**, 2207. (h) Yang, W.-Q.; Kitahara, T. *Tetrahedron* **2000**, *56*, 1451. (i) Hu, T.-S.; Wu, Y.-L.; Wu, Y. *Org. Lett.* **2000**, *2*, 887. (j) Yu, Q.; Yao, Z.-J.; Chen, X.-G.; Wu, Y.-L. *J. Org. Chem.* **1999**, *64*, 2440. (k) Yu, Q.; Wu, Y.; Ding, H.; Wu, Y.-L. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1183. (l) Hu, T.-S.; Yu, Q.; Lin, Q.; Wu, Y.-L.; Wu, Y. *Org. Lett.* **1999**, *1*, 399. (m) Marshall, J. A.; Jiang, H. *J. Org. Chem.* **1999**, *64*, 971. (n) Sinha, A.; Sinha, S. C.; Sinha, S. C.; Keina, E. *J. Org. Chem.* **1999**, *64*, 2381. (o) Sinha, S. C.; Sinha, S. C.; Keinan, E. *J. Org. Chem.* **1999**, *64*, 7067. (p) Wang, Z.-M.; Tian, S.-K.; Shi, M. *Tetrahedron Lett.* **1999**, *40*, 977. (q) Wang, Z.-M.; Tian, S.-K.; Shi, M. *Tetrahedron: Asymmertry* **1999**, *10*, 667. (r) Takahahi, S.; Nakata, T. *Tetrahedron Lett.* **1999**, *40*, 723; **1999**, *40*, 727. (s) Hanessian, S. Grillo, T. A. *J. Org. Chem.* **1998**, *63*, 1049. (t) Marshall, J. A.; Jiang, H. *Tetrahedron Lett.* **1998**, *39*, 1493. Marshall, J. A.; Jiang, H.; *J. Org. Chem.* **1998**, *63*, 7066. Marshall, J. A. and Hinkle, K. W. *Tetrahedron Lett.* **1998**, 39, 1303. (u) Makabe, H.; Tanaka, A.; Oritani T. *Tetrahedron* **1998**, *54*, 6329. (v) Sinha, S. C.; Sinha, A.; Sinha, S. C.; Keinan, E. *J. Am. Chem. Soc.* **1998**, *120*, 4017. Yazbak, A.; Sinha, C. C.; Keinan, E. *J. Org. Chem.* **1998**, *63*, 5863. Neogi, P.; Doundoulakis, T.; Yazak, A.; Sinha, S. C.; Sinha, S. C.; Keinan, E. *J. Am. Chem. Soc.* **1998**, *120*, 11279. (w) Schans, S. E.; Branact, J.; Jacobson E. N. *J. Org. Chem.* **1998**, *63*, 4876.

(2) Yao, Z.-J.; Wu, Y.-L. *Tetrahedron Lett.* **1994**, *35*, 157. Yao, Z.-J.; Wu, Y.-L. *J. Org. Chem.* **1995**, *60*, 1170.

(3) Zeng, B.-B.; Wu, Y.; Yu, Q.; Wu, Y.-L.; Li, Y.; Chen, X.-G. *Angew. Chem., Int. Ed.* **2000**, *39*, 1934.

(4) Chen, Y.; Yu, D.-Q. *J. Nat. Prod.* **1996**, *59*, 507.

(5) Pan, X.-P.; Yu, D.-Q. *Acta Pharm. Sin.* **1997**, *32*, 286. Chen, Y.; Chen, R. Y.; Yu, D. Q. *Phytochemistry*, **1996**, *43*, 793. Zheng, X. C.; Yang, R. Z.; Xu, R. S.; Qin, G. W. *Acta Botan. Sin.* **1994**, *36*, 557.

10.1021/jo005643b CCC: $20.00
Published on Web 12/21/2000

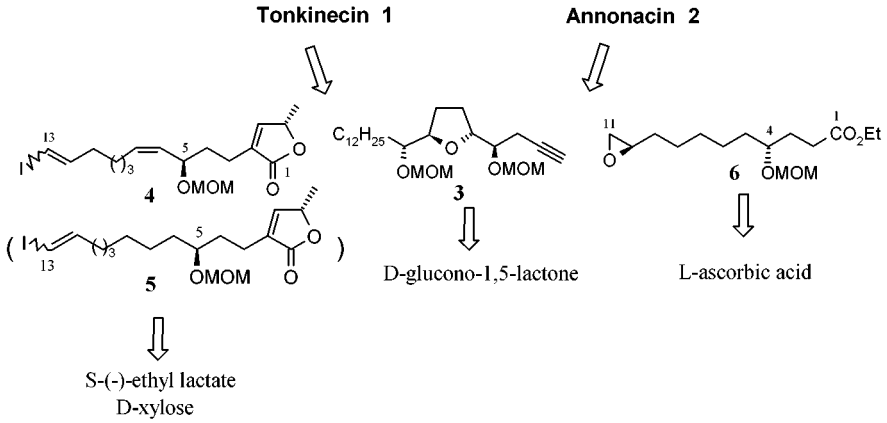


Figure 1. Retrosynthetic analysis of **1** and **2**.

number of carbon in the alkyl chain between the THF and the γ-lactone and the number as well as position of the hydroxyl group on it, which are critical[1a] to the biological activities of the acetogenins.

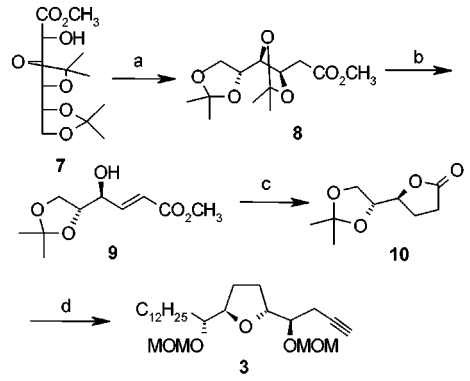
Our retrosynthetic strategy is illustrated in Figure 1. A key feature of our approach is use of alkyne **3** as a common key intermediate to both **1** and **2**. Thus, the carbon skeleton of **1** can be constructed by Pd(0)-catalyzed cross coupling reaction of **3** with vinyl iodide **4** or **5**, while that of **2** can be obtained by epoxide opening reaction between **3** and **6**. The intermediates **3**, **4**, **5**, and **6** were prepared from D-glucono-δ-lactone, D-xylose, *S*-(−)ethyl lactate and L-ascorbic acid, respectively. The introduction of butenolide moiety of **1** was arranged at an early stage of the synthesis. However, butenolide segment of **2** was introduced at the end of its synthesis to avoid γ-epimerization of the butenolide segment that might occur in basic media,[1m,7] because a relative strong base was required to prepare **6**.

Results and Discussion

Synthesis of Alkyne 3. Deoxygenation of α-hydroxyl ester **7**,[8] which was derived from readily available D-glucono-1,5-lactone, by treatment with Ph_3P/I_2/imidazole in toluene[9] gave ester **8** in 69% yield (Scheme 1). The ester **8** was then treated with LiHMDS in THF to give α,β-unsaturated ester **9** in 97% yield. Hydrogenation followed by acid-catalyzed ring closure produced lactone **10** in 86% yield. Then compound **10** was converted to alkyne **3** via a multistep procedure described previously[1k,l] by us.

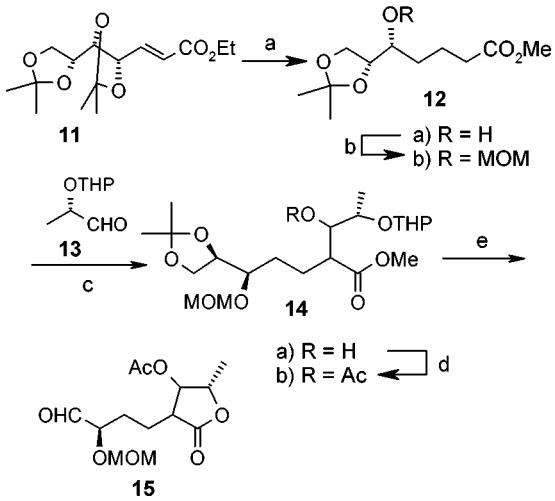
Synthesis of Butenolide 4. The two stereogenic centers of **4** were related to D-xylose and (*S*)-ethyl lactate, respectively (Scheme 2). Thus, α,β-unsaturated ester **11**[10] was treated with Mg in methanol to give δ-hydroxyl ester **12a** in 61% yield, which was protected as MOM ether **12b**. Condensation of enolate derived from **12b** with (*S*)-OTHP lactal **13**[2] led to aldol adduct **14a** as a mixture of diastereoisomers in 71% yield. After acetylation of **14a**, compound **14b** was subjected to periodic acid in ether to afford aldehyde **15** in 76% yield.

Scheme 1[a]



[a] Reagents and conditions: (a) PPh_3, I_2, imidazole, toluene, reflux, 69%; (b) LiHMDS, THF, −78 °C, 95%; (c) (i) H_2/Pd−C, MeOH; (ii) acetone, *p*-TsOH (cat.), 86%; (d) ref 1k, l.

Scheme 2[a]

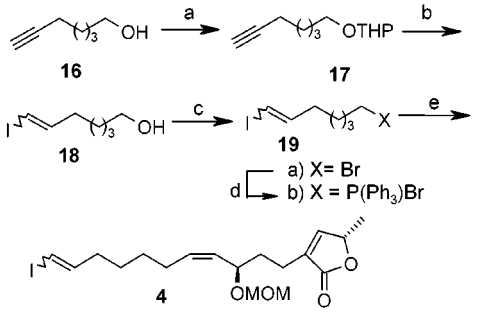


[a] Reagents and conditions: (a) Mg, CH_3OH, reflux, 61%; (b) MOMCl, $^iPr_2NEt$, CH_2Cl_2, 0 °C → rt, 98% (c) LDA, THF−HMPA (6:1,v/v), −78 °C; then **13**, 71%; (d) Ac_2O, Py, rt, 90%; (e) H_5IO_6, Et_2O, rt, 76%.

The synthesis of **19b** (Scheme 3) started with hept-6-yn-1-ol (**16**), which was prepared[10] in two steps from prop-2-yn-1-ol and 1-bromobutane. Protection of **16**, hydrostannation, and iodolysis, and finally removal of the THP group led to vinyl iodide **18** in 89% yield based on **16**. The primary alcohol was converted first to bromide **19a** before being transformed into the corresponding phos-

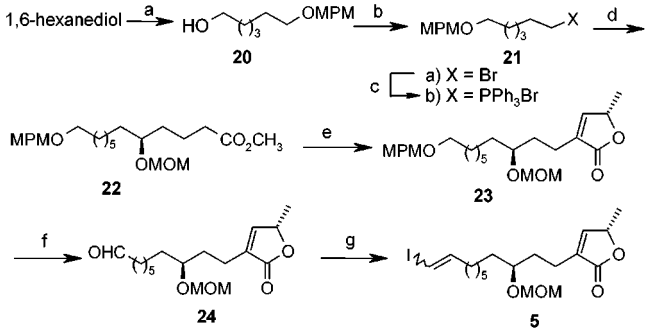
(6) McCloud, T. G.; Smith, D. L.; Chang, C.-J.; Cassady, J. M. *Experientia*. **1987**, *43*, 947.
(7) Duret, P.; Figadere, B.; Hocquemiller, R.; Cave, A. *Tetrahedron Lett*. **1997**, *38*, 8849.
(8) Regeling, H.; Rouville, E.; Chittenden, G. J. F. *Recl. Trav. Chim. Pays-Bas* **1987**, *106*, 461.
(9) Rauter, A. P.; Fernandes, A. C.; Figueiredo, J. A. *J. Carbohydr. Chem*. **1998**, *17*, 1037.
(10) Yadav, J. S.; Barma, D. K. *Tetrahedron* **1996**, *52*, 4457.

Scheme 3[a]



[a] Reagents and conditions: (a) DHP, PPTS (cat.), CH_2Cl_2, rt, 95%; (b) (i) Bu_3SnH, AIBN (cat.), 130 °C, 2 h, then I_2; (ii) PTSA (cat.), CH_3OH, rt, 94%; (c) PPh_3, CBr_4, CH_2Cl_2, 0 °C → rt, 90%; (d) PPh_3, CH_3CN, reflux, quant; (e) LiHMDS, THF/HMPA (6:1,v/v), −78 °C, then **15**, 31%.

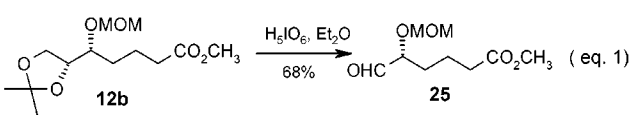
Scheme 4[a]



[a] Reagents and conditions: (a) NaH, DMF, then *p*-methoxylbenzyl chloride, 44%; (b) PPh_3, CBr_4, CH_2Cl_2, 93%; (c) PPh_3, CH_3CN, reflux, quant; (d) (i) NaHMDS, THF, 0 °C, then −78 °C, **25**, 64%; (ii) H_2, Pd/C, EtOH, 97%; (e) (i) −78 °C, THF, LDA, then **13**, 96%; (ii) AcOH/THF/H_2O (4:2:1), 55 °C; (iii) $(CF_3CO)_2O$, Et_3N, 66% for two steps; (f) (i) DDQ, CH_2Cl_2/H_2O (v/v 18:1), 78%; (ii) Dess−Martin periodinane, CH_2Cl_2, 96%; (g) CHI_3, $CrCl_2$, THF, 75%.

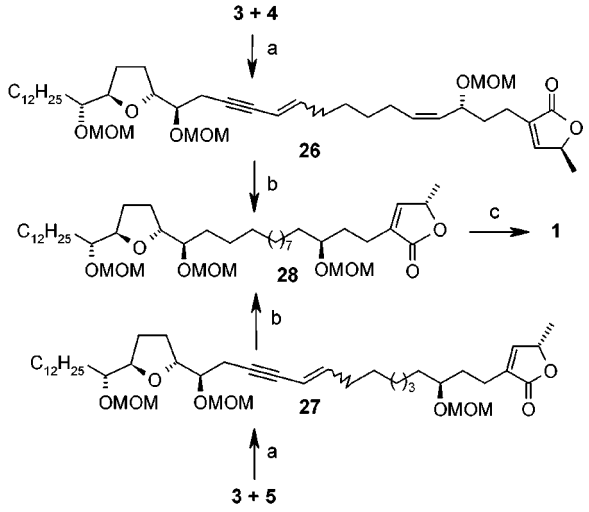
phonium salt **19b**. The following coupling of **19b** with aldehyde **15** and concomitant elimination of acetate ester afforded the butenolide **4** in 31% yield.

Second Approach to C1−C13 Segment of 1 (Synthesis of Butenolide 5). A possible reason for the rather poor yield for Wittig reaction of **19b** with **15** is that the vinyl iodide is eliminated under the basic conditions to give a terminal alkyne. To overcome this drawback and also avoid use of tributytin hydride, an alternative route (Scheme 4) to the C1−C13 segment of **1** was then explored. Thus, 1,6-hexanediol was protected as mono-PMB ether **20** in 44% yield, which was converted to bromide and then to phosphonium salt **21b**. Wittig reaction of the latter with aldehyde **25** prepared from **12b** (eq 1) followed by hydrogenation gave ester **22** in 62% yield over two steps. Subsequent introduction[1m,2] of the



butenolide unit involved three steps: (1) adol reaction of **22** with aldehyde **13**; (2) acid-catalyzed THP cleavage and concurrent ring closure; (3) *β*-elimination in the presence of F_3CCO_2H and NEt_3. Cleavage of PMB group in **23** and oxidation of the resulting alcohol afforded

Scheme 5[a]



[a] Reagent and conditions: (a) $(PPh_3)_2PdCl_2$, CuI, Et_3N, rt, 93% from **26**, 86% from **27**; (b) $TsNHNH_2$, NaOAc, DME, reflux, 65%; (c) $BF_3{\cdot}Et_2O$, Me_2S, 0 °C, 86%.

aldehyde **24**, which was treated with CHI_3 and $CrCl_2$ to produce vinyl iodide **5** in 75% yield as a 4:1 mixture of *E*/*Z* isomers.

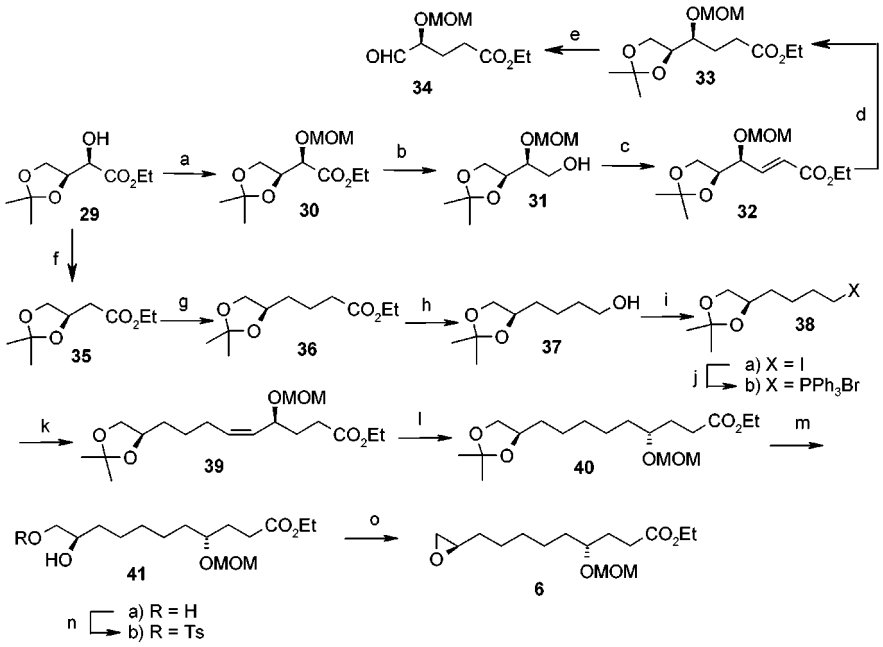
Synthesis of Tonkinecin 1. Treatment of vinyl iodides **4** and **5** with terminal alkyne **3** in the presence of $(PPh_3)_2PdCl_2$ and CuI in NEt_3 gave **26** and **27** in 93% and 86% yield, respectively. Subsequent hydrogenation of **26** or **27** with diimide[12] produced precursor **28** (Scheme 5). Finally, cleavage of the MOM ethers with $BF_3.OEt_2$ in $SMe_2$13 afford **1** as a waxy solid in 86% yield. The spectral data of **1** were identical with the reported ones.[4]

Synthesis of Epoxide 6 (C1−C11 Segment of 2). The synthesis of epoxide **6** is summarized in Scheme 6. Protection of α-hydroxyl ester **29**[14] derived from L-ascorbic acid as MOM ether followed by LAH reduction gave **31** in 84% yield for two steps. **31** was converted to α,*β*-unsaturated ester **32** by Swern oxidation followed by Wittig reaction. It is noteworthy that at the Swern oxidation step, the choice of base used was crucial. Considerable epimerization at the α position of the resultant aldehyde was observed with NEt_3 as base, which was commonly used in Swern oxidation. However, with $^iPr_2NEt$ as base, this problem was overcome. Catalytic hydrogenation afforded **33** in 97% yield. Subsequent removal of the isopropylidene group and oxidative cleavage of the resulting diol with sodium periodate furnished aldehyde **34** in 73% yield.

Compound **29** was converted to ester **35** according to a known[15] procedure. Two-carbon chain elongation of **35** to give **36** was realized in 69% yield via reduction of **35** with LAH, Swern oxidation followed by Wittig reaction, and finally catalytic hydrogenation. Treatment of **36** with LAH afforded alcohol **37** in 95% yield, which was

(11) Brandsma, L. *Preparative acetylenic chemistry*, 2nd ed.; Elsevier: Amsterdam, 1988; p 245.
(12) Marshall, J. A.; Hinkle, K. W., *J. Org. Chem.* **1997**, *62*, 5989.
(13) Naito, H.; Kawahara, E.; Maruta, K.; Maeda, M.; Sasaki, S. *J. Org. Chem*, **1995**, *60*, 4419.
(14) Wei, C. C.; De Bernardo, S.; Tengi, J. P.; Borgese, J.; Weigele, M. *J. Org. Chem*. **1985**, *50*, 3462. Jung, M. E.; Shaw, T. J. *J. Am. Chem. Soc.* **1980**, *102*, 6304.
(15) Tanaka, A.; Yamashida, K. *Synthesis* **1987**, 570.

Scheme 6[a]

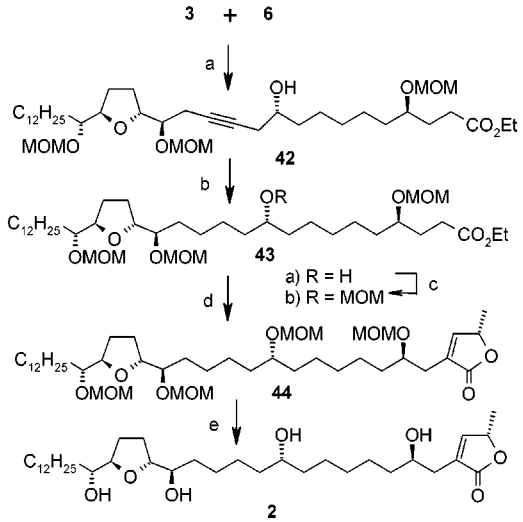


[a] Reagents and conditions: (a) MOMCl, $^{i}Pr_2NEt$, CH_2Cl_2, 0 °C to room temperature, 88%; (b) LAH, THF, 0 °C to room temperature, 96%; (c) (i) oxalyl chloride, DMSO, $^{i}Pr_2NEt$; (ii) $PPh_3{=}CHCO_2Et$, CH_2Cl_2, reflux, 81%; (d) H_2/Pd−C, EtOH, rt, 97%; (e) (i) 60% AcOH, 45 °C, 1 h; (ii) $NaIO_4$, CH_2Cl_2/H_2O, rt, 73% for two steps; (f) Reference 14. (g) (i) LAH, THF, 0 °C to rt; (ii) oxalyl chloride, DMSO, Et_3N; (iii) $PPh_3{=}CHCO_2Et$, CH_2Cl_2, reflux, 73% for three steps; (iv) H_2/Pd−C, EtOH, rt, 95%; (h) LAH, THF, 0 °C to rt, 95%; (i) (i) *p*-TsCl, Et_3N, CH_2Cl_2, 0 °C to rt, 94%; (ii) NaI, acetone, rt, 98%; (j) PPh_3, Na_2CO_3, CH_3CN, quantitative; (k) NaHMDS, THF, 0 to −78 °C then **34**, 81%; (l) H_2/Pd−C, $NaHCO_3$, EtOH, rt, 97%; (m) (i) 60% aq HOAc, 97%; (n) *p*-TsCl, Et_3N, Bu_2SnO (cat.), CH_2Cl_2, 81%; (o) DBU, CH_2Cl_2, rt, 97%.

converted to tosylate and then to iodide **38a**. The latter was reacted with PPh_3 to give phosphonium salt **38b**. Treatment of **38b** with NaHMDS and then aldehyde **34** afforded **39** in 81% yield, which, after hydrogenation, gave ester **40** in 97% yield. Hydrolysis of the acetonide group afforded diol **41a**, which was converted to primary tosylate **41b** in 81% yield by Bu_2SnO-catalyzed[16] tosylation. Treatment of **41b** with DBU in methylene chloride gave epoxide in 97% yield.**Synthesis of Annonacin (2).** Successful accomplishment of epoxide **6** set the stage for the construction of carbon skeleton of **2**. Thus, the lithiated derivative of alkyne **3** was reacted with epoxide **6** in the presence of $BF_3{\cdot}Et_2O$ to afford alkynol **42** in 77% yield. To our surprise, catalytic hydrogenation of **42** over Pd/C led to a mixture of ca. 1:1 ratio of the desired alcohol **43a** and 10-deoxgenated byproduct. However, substitution of Pd/C with PtO_2 as catalyst afforded **43a** in 93% yield, which was then protected as MOM ether **43b** in 95% yield. In a similar sequence to that from **22** to **23**, **43a** was converted to butenolide **44** in 41% yield. The final stage of the synthesis, deprotection of the MOM ethers of **44**, was effected in 85% yield with $BF_3{\cdot}Et_2O$ in the presence of Me_2S. The spectral data of the resulting product **2** were in accord with those reported for the natural product.[6]

In conclusion, total synthesis of tonkinecin and annonacin has been achieved via convergent routes using readily available carbohydrates and hydroxyl acid as starting materials. The strategy described herein should be applicable to various analogues of acetogenins. Further biological evaluation of **1** and **2** is undergoing.

Scheme 7[a]



[a] Reagent and conditions: (a) BuLi, THF, −78 °C, 1 h, then $BF_3{\cdot}Et_2O$, 30 min then **4**, 77%; (b) PtO_2, EtOH, rt, 93%; (c) MOMCl, $^{i}Pr_2NEt$, CH_2Cl_2, 0 °C to rt, 95%; (d) (i) LDA, THF, −78 °C, then O-THP lactaldehyde; (ii) HOAc/THF/H_2O (4:2:1); (iii) $(CF_3CO)_2O$, Et_3N, 0 °C to rt, 41% for three steps; (e) $BF_3{\cdot}Et_2O$, Me_2S, 0 °C to rt, 85%.

Experimental Section

General Methods. NMR spectra were recorded in $CDCl_3$ at 300, 400 and 600 MHz, respectively. IR spectra were recorded on a Perkin-Elmer 983 or IR-440 spetrophotomer. Mass spectra were obtained on an HP 5989A Mass spectrometer. Optical rotations were measured on a Perkin-Elmer 241 MC autopol polarimeter. Elemental analyses were carried out at the Microanalytic Laboratory of Shanghai Institute of Organic Chemistry. Flash column chromatography was performed on silica gel (10−40 μm).

(16) Martinelli, M. J.; Nayyar, N. K.; Moher, E. D.; Dhokte, U. P.; Pawlak, J. M.; Vaidyanathan, R. *Org. Lett.* **1999**, *1*, 447.

Methyl (2*RS*,5*R*,6*R*,1′*RS*,2′*S*)-2-(1′-Hydroxy-2′-tetrahydropyranyloxyprop-1′-yl)-6,7-dihydroxy-6,7-*O*-isopropylidene-5-methoxymethoxyheptanoate (14a). To a solution of diisopropylamine (0.2 mL, 1.53 mmol) in THF (8 mL) at 0 °C was added BuLi (0.6 mL, 1.5 mmol). The mixture was stirred at 0 °C for 10 min and cooled to −78 °C and then was added HMPA (1 mL). The reaction mixture was stirred at −78 °C for 30 min, and then a solution of ester **12b** (0.388 g, 1.22 mmol) in THF (3 mL) was added. After another 30 min, a solution of aldehyde **13** (0.220 g, 1.39 mmol) in THF (2 mL) was added. The reaction mixture was stirred at −78 °C for 2 h, quenched with saturated aqueous NH_4Cl solution, and extracted with ether. The extracts were washed with brine and dried over Na_2SO_4. After filtration and concentration, the crude product was purified by column chromatography to afford **14a** (0.376 g, 71%) as a mixture of diasteroisomers: IR (film) 3463, 2942, 1734 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.79 (m, 1H), 4.66 (m, 1H), 4.60 (m, 1H), 4.18 (m, 1H), 3.98 (m, 1H), 3.86 (m, 1H), 3.80−3.42 (m, 5H), 3.69 (s, 3H), 3.39, 3.38 (s, s, 3H), 2.62, 2.50 (m, m, 1H), 1.97 (m, 1H), 1.90−1.62 (m, 3H), 1.40 (s, 3H), 1.34 (s, 3H), 1.59−1.11 (m, 9H); EIMS (*m*/*z*) 403 (M^+ − CH_3O, 0.57), 101 (17.25), 85 (THP, 100), 45 (42.21).

Methyl (2*RS*,5*R*,6*R*,1′*RS*,2′*S*)-2-(1′-Acetoxy-2′-tetrahydropyranyloxyprop-1′-yl)-6,7-dihydroxy-6,7-*O*-isopropylidene-5-methoxymethoxyheptanoate (14b). A mixture of alcohol **14a** (4.500 g, 10.36 mmol) and acetic anhydride (5 mL) in pyridine (25 mL) was stirred for 16 h at room temperature, diluted with ether (100 mL), washed with 10% aqueous HCl solution, H_2O, and brine, and dried over Na_2SO_4. The solvents were evaporated under reduce pressure, and the residue was purified by column chromatography to afforded **14b** (4.451 g, 90%) as a colorless oil: IR (film) 2942, 1740, 1372 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.20 (m, 1H), 4.79 (m, 1H), 4.65 (m, 1H), 4.60 (m, 1H), 4.13 (m, 1H), 3.95 (m, 1H), 3.90−3.40 (m, 5H), 3.66 (m, 3H), 3.38 (m, 3H), 2.82−2.58 (m, 1H), 3.04 (m, 3H), 1.70 (m, 5H), 1.58−1.05 (m, 8H), 1.38 (s, 3H), 1.33 (s, 3H); EIMS (*m*/*z*) 85 (73.87), 101 (64.49). Anal. Calcd for $C_{23}H_{40}O_{10}$: C, 57.97; H, 8.46. Found: C, 57.84; H, 8.58.

(2*R*,3′*RS*,4′*RS*,5′S)-4-(4′-Acetoxy-5′-methyl-2′-oxotetrahydrofuran-3′-yl)-2-methoxymethoxybutanal (15). To a solution of compound **14b** (1.113 g, 2.34 mmol) in ether (12 mL) was added periodic acid (1.065 g, 4.67 mmol). The reaction mixture was stirred for 20 h at room temperature, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography to give **15** (0.511 g, 76%) as a colorless oil: IR (film) 2942, 2826, 1771, 1736; ^1H NMR (300 MHz, $CDCl_3$) δ 9.61 (d, J = 1.7 Hz, 1H), 5.12 (m, 0.25H), 4.89 (dd, J = 6.0, 5.9 Hz, 0.85H), 4.71 (m, 2H), 4.49, 4.37 (m, m, 1H), 3.91 (m, 1H), 3.40 (s, 3H), 2.70 (m, 1H), 2.10 (m, 3H), 1.85 (m, 4H), 1.39 (m, 3H); MS (*m*/*z*) 289 (MH^+, 0.50), 227 (71.46), 197 (80.08), 167 (53.72).

(*EZ*)-7-Iodohept-6-en-1-ol (18). To a solution of alkynol **16** (1.370 g, 0.012 mol) in CH_2Cl_2 (30 mL) were added DHP (1.541 g, 0.018 mol) and PPTS (0.129 g). The mixture was stirred for 12 h at room temperature, diluted with ether (50 mL), washed with H_2O, saturated aqueous $NaHCO_3$ solution, and brine, and dried over Na_2SO_4. Removal of the solvent under reduced pressure and purification by column chromatography afforded the product (2.290 g, 95%) as a colorless oil. A mixture of the above product (2.290 g, 0.012 mol), AIBN (ca. 0.1 g), and tributytin hydride (4.7 mL, 0.017 mol) was stirred for 2.5 h at 130 °C and then cooled to 0 °C. To it was added ether (20 mL) and then iodine (3.800 g, 0.015 mol) in portions. The reaction mixture was stirred at room temperature overnight, and then solid potassium fluoride (1.200 g, 0.021 mol) and H_2O (1.5 mL) were added to destroy excess tributytin hydride. After filtration, the filtrate was washed with aqueous $Na_2S_2O_3$ solution and brine and dried over Na_2SO_4. The solvent was evaporated under reduced pressure, and the residue was dissolved in methanol. To the mixture was added *p*-toluenesulfonic acid monohydrate (0.222 g). The reaction mixture was stirred for 24 h at room temperature and neutralized with solid K_2CO_3 (1.9 g). Filtration, removal of the solvent, and purification by column chromatography afforded **18** (2.631 g, 94%) as a 4:1 mixture of *E* and *Z* isomers: IR (film) 3342, 3047, 2930, 2856, 1604, 945 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.49 (dt, J = 14.3, 7.1 Hz, 0.8H, from one olefinic proton in the trans isomer), 6.17 (m, 0.4H, from two olefinic protons in the cis isomer), 5.97 (ddd, J = 14.3, 2.2, 1.4 Hz, 0.8H, from one proton in the trans isomer), 3.62 (m, 2H), 2.18−1.95 (m, 2H), 1.61−1.25 (m, 6H); EIMS (*m*/*z*) 127 (6.15), 113 (9.23).

(*EZ*)-7-Bromo-1-iodohept-1-ene (19a). To a mixture of alcohol **18** (2.605 g, 0.010 mol) and carbon tetrabromide (4.320 g, 0.013 mol) in CH_2Cl_2 (10 mL) at 0 °C was added a solution of triphenylphosphine (4.264 g, 0.016 mol) in CH_2Cl_2 (10 mL). The reaction mixture was stirred at room temperature for 3 h, concentrated under reduced pressure, and purified by column chromatography to afford **19a** (2.942 g, 90%) as a colorless oil. IR (film) 3045, 3004, 2930, 2854, 1605 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.50 (dt, J = 14.6, 7.1 Hz, 0.78H, from olefinic proton in the trans isomer), 6.17 (m, 0.44H, from two olefinic protons in the cis isomer), 6.00 (dt, J = 14.3, 1.4 Hz, 0.78H, from olefinic proton in the trans isomer), 3.41 (t, J = 6.9 Hz, 0.44H), 3.40 (t, J = 6.9, 1.56H), 2.16 (m, 0.44H), 2.06 (m, 1.56H), 1.85 (m, 2H), 1.43 (m, 4H); EIMS (*m*/*z*) 303 (21.99), 301 (22.02), 95 (100.00), 127 (4.79). Anal. Calcd for $C_{17}H_{12}BrI$: C, 27.75; H, 3.99. Found: C, 27.62; H, 4.02.

(4′*Z*,10′*EZ*,5*S*,3′*R*)-3-(11′-Iodo-3′-methoxymethoxyundeca-4′,10′-dien-1′-yl)-5-methylfuran-2(5*H*)-one (4). A mixture of bromide **19a** (0.391 g, 1.23 mmol) and PPh_3 (0.629 g, 2.45 mmol) in CH_3CN (8 mL) was stirred at 90 °C for 24 h, concentrated under reduced pressure and washed with Et_2O several times. The phosphonium salt **19b** was dried in vacuo, dissolved in THF (8 mL) and treated with LiHMDS (prepared from 0.52 mL of BuLi (1.30 mmol) and 0.3 mL of HMDS (1.42 mmol)) in THF (2 mL) at 0 °C. The orange solution was stirred at 0 °C for 30 min and cooled to −78 °C, and then HMPA (1.5 mL) was added. The mixture was stirred another 30 min, and a solution of aldehyde **15** (0.265 g, 0.92 mmol) in THF (2.5 mL) was added. The reaction mixture was stirred for 2 h from −78 °C to room temperature, quenched with saturated aqueous NH_4Cl solution, and extracted with ether. The extracts were washed with brine and dried over Na_2SO_4. Concentration and chromatography afforded butenolide **4** (0.123 g, 31%) as a colorless oil: $[\alpha]_D$ +89.3 (*c* 1.22 $CHCl_3$); IR (film) 2929, 1747, 1651, 1449, 954, 922 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.02 (s, 1H), 6.49 (dt, J = 14.3, 7.1 Hz, 0.83H, from one olefinic proton of trans isomer), 6.17 (m, 0.33H, from two olefinic protons of cis isomer), 5.99 (d, J = 14.3 Hz, 0.83H, from one olefinic proton of trans isomer), 5.61 (dt, J = 11.0, 7.2 Hz, 1H), 5.23 (m, 1H), 5.01(dq, J = 1.8, 6.6 Hz, 1H), 4.66 (d, J = 6.9 Hz, 1H), 4.48 (d, J = 6.9 Hz, 1H), 4.39 (m, 1H), 3.37 (s, 3H), 2.36 (m, 2H), 2.07 (m, 4H), 1.88 (m, 1H), 1.72 (m, 1H), 1.41 (d, J = 6.6 Hz, 3H), 1.45−1.31 (m, 4H); EIMS (*m*/*z*) 389 ([M^+-MOM], 6.27), 45 (100.00); HRMS calcd for $C_{16}H_{22}O_3I$ (M − MOM) 389.0612, found 389.0625.

1-Bromo-6-*p*-methoxybenzyloxyhexane (21a). To a suspension of 60% NaH (0.915 g, 0.022 mol) in DMF (22 mL) at −20 °C was added a solution of 1,6-hexanediol (2.364 g, 0.020 mol) in DMF (14 mL). The mixture was stirred at the same temperature for 30 min, and a solution of *p*-methoxybenzyl chloride (3.451 g, 0.022 mol) in DMF (7 mL) was added. The reaction mixture was stirred at −20 °C for 2 h and then pooled into ice−water (100 mL), extracted with ether. The extracts were washed with brine and dried over Na_2SO_4. The solvent was removed, and the residue was purified by chromatography to afford alcohol **20** (2.080 g, 44%) as a colorless oil: IR (film) 3393, 2935, 2860, 1614, 1587, 1514 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.25 (d, J = 8.5 Hz, 2H), 6.87 (d, J = 8.5 Hz, 2H), 4.42 (s, 2H), 3.79 (s, 3H), 3.62 (t, J = 6.5 Hz, 2H), 3.43 (t, J = 6.6 Hz), 1.56 (m, 4H), 1.37 (m, 4H); MS (*m*/*z*) 238 (M^+, 3.46), 137 (59.35), 121 (100.00), 77 (9.31).

To a mixture of alcohol **20** (0.800 g, 3.36 mmol) and carbon tetrabromide (1.337 g, 4.03 mmol) in CH_2Cl_2 at 0 °C was added a solution of PPh_3 (1.319 g, 5.03 mmol) in CH_2Cl_2 (3 mL). The reaction mixture was stirred at room temperature for 1 h, concentrated under reduced pressure and purified by column chromatography to afford bromide **21b** (0.941 g, 93%): IR (film) 2930, 2857, 1601, 1580 cm^{-1}; ^1H NMR (300 MHz, CD_3Cl) δ 7.25 (d, J = 8.7 Hz, 2H), 6.87 (d, J = 8.7 Hz, 2H), 4.42 (s,

2H), 3.80 (s, 3H), 3.43 (t, J = 6.6 Hz, 2H), 3.39 (t, J = 6.9 Hz, 2H), 1.85 (m, 2H), 1.41 (m, 4H); EIMS (*m*/*z*) 302 (2.52), 301 (1.38), 300 (2.70), 137 (8.07), 121 (100), 77 (7.50).

Methyl (5*R*)-5-Methoxymethoxy-6-oxo-hexanoate (25). To a solution of **12b** (1.043 g, 3.77 mmol) in ether (23 mL) was added periodic acid (1.800 g, 7.90 mmol), and the reaction mixture was stirred at room temperature for 12 h and filtered. The filtrate was washed with H_2O and brine and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the residue was purified by column chromatography to afford aldehyde **25** (0.527 g, 68%) as a colorless oil: $[\alpha]_D$ +34.5 (*c* 1.02, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.62 (d, J = 1.7 Hz, 1H), 4.72 (d, J = 6.9 Hz, 1H), 4.68 (d, J = 6.9 Hz, 1H), 3.98 (m, 1H), 3.67 (s, 3H), 3.37 (s, 3H), 2.33 (t, J = 7.4 Hz, 2H), 1.75 (m, 2H), 1.50 (m, 2H).

Methyl (5*S*)-5-Methoxymethoxy-12-*p*-methoxybenzyloxydodecanoate (22). A mixture of bromide **21a** (0.482 g, 1.60 mmol) and PPh_3 (0.838 g, 0.32 mmol) in CH_3CN (12 mL) was stirred at 90 °C for 2 days, concentrated under reduced pressure, and washed with ether several times. The phosphonium salt obtained was dried in vacuo, dissolved in THF (14 mL), and treated with NaHMDS (1.6 mL, 1 M solution in THF, 1.6 mmol) at 0 °C. The orange solution was stirred at 0 °C for 30 min and then cooled to −78 °C, and a solution of aldehyde **25** (0.205 g, 1.00 mmol) in THF (8 mL) was added. The reaction mixture was stirred at −78 °C for 2 h, quenched with brine, and extracted with ether. The extracts were washed with H_2O and brine and dried over Na_2SO_4. The solvents were removed under reduced pressure, and the residue was purified by column chromatography to afford product (0.260 g, 64%) as a colorless oil: $[\alpha]_D$ +65.7 (*c* 1.30, $CHCl_3$); IR (film) 2933, 2855, 1736, 1610, 1585, 1510 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25 (d, J = 6.9 Hz,2H) 6.88 (d, J = 6.9 Hz, 2H) 5.59 (dt, J = 10.9, 7.6 Hz, 1H), 5.20 (dd, J = 10.9, 9.4 Hz, 1H), 4.66 (d, J = 6.6 Hz, 1H), 4.47 (d, J = 6.6 Hz, 1H), 4.43 (s, 2H), 4,38 (m, 1H), 3.81 (s, 3H), 3.67 (s, 3H), 3.43 (t, J = 6.5 Hz, 2H), 3.36 (s, 3H), 2.34 (t, J = 7.2 Hz, 2H), 1.75−1.55 (m, 6H), 1.55−1.30 (m, 6H) EIMS (*m*/*z*) 363 (M^+ − MOM, 0.90), 346 (1.89), 137 (11.52), 121 (100.00), 45 (16.24). Anal. Calcd for $C_{23}H_{36}O_6$: C, 67.62; H, 8.88. Found: C, 67.76; H, 9.03.

To a solution of the above product (0.170 g, 0.42 mmol) in 95% ethanol (4 mL) were added 10% Pd/C (0.025 g) and triethylamine (0.17 mL, 0.83 mmol). The mixture was stirred at room temperature for 3 h under 1 atm of pressure of hydrogen, filtrated through Celite, and concentrated to give crude product, which was purified by column chromatography to afford **22** (0.165 g, 97%) as a colorless oil: $[\alpha]_D$ +4.29 (*c* 0.81, $CHCl_3$); IR (film) 2930, 2853, 1736, 1610, 1510, 1460 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27 (d, J = 8.8 Hz, 2H), 6.89 (d, J = 8.8 Hz, 2H), 4.65 (s, 2H), 4.44 (s, 2H), 3.82 (s, 3H), 3.68 (s, 3H), 3.54 (m, 1H), 3.42 (t, J = 6.6 Hz, 2H), 3.39 (s, 3H), 2.34 (t, J = 7.4 Hz), 1.80−1.45 (m, 8H), 1.31 (brs, 8H); EIMS (*m*/*z*) 365 (M^+ − MOM, 6.23), 137 (13.82), 121 (100.00), 77 (3.86), 45 (25.77).

(5*S*,3′*S*)-3-(3′-Methoxymethoxy-10′-*p*-methoxybenzyloxydecan-1′-yl)-5-methylfuran-2(5*H*)-one (23). To a solution of diisopropylamine (0.28 mL, 1.98 mmol) in THF (4 mL) at 0 °C was added BuLi (0.64 mL, 1.6 M solution in hexane, 1.02 mmol). The mixture was stirred at 0 °C for 10 min and then cooled to −78 °C, and a solution of ester **22** (0.210 g, 0.51 mmol) in THF (4 mL) was added. After 40 min, a solution of aldehyde **13** (0.162 g, 1.02 mmol) in THF (3 mL) was added. The reaction was stirred at −78 °C for 1.5 h, quenched with saturated aqueous NH_4Cl solution, and extracted with ether. The extracts were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography to afford aldol product (0.280 g, 96%) as a mixture of diastereoisomers. The mixture was dissolved in AcOH/THF/H_2O (10 mL, 4:2:1), stirred at 55 °C for 2 h, and concentrated in vacuo. To a mixture of the residue (0.180 g) and triethylamine (0.6 mL, 4.27 mmol) in CH_2Cl_2 (18 mL) at 0 °C was added trifluoroacetic anhydride (0.36 mL, 2.54 mmol). The reaction mixture was stirred at room temperature for 20 h, diluted with ether, and washed with saturated aqueous $NaHCO_3$ solution and brine, dried over Na_2SO_4. Removal of the solvents gave crude product which, after chromatography, afforded **23** (0.092 g, 60%) as a colorless oil: $[\alpha]_D$ +25.1 (*c* 0.59, $CHCl_3$); IR (film) 2933, 2857, 1756, 1614, 1580, 1514, 1465, 1098, 1035 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27 (d, J = 8.6 Hz, 2H), 7.03 (s, 1H), 6.89 (d, J = 8.6 Hz, 2H), 5.01 (m, 1H), 4.68 (d, J = 7.1 Hz, 1H), 4.65 (d, J = 7.1 Hz, 1H), 4.44 (s, 2H), 3.81 (s, 3H), 3.57 (m, 1H), 3.44 (t, J = 6.6 Hz, 2H), 3.40 (s, 3H), 2.36 (m, 2H), 1.75 (m, 2H), 1.70−1.46 (m, 4H), 1.42 (d, J = 6.6 Hz, 3H), 1.31 (brs, 8H); EIMS (*m*/*z*) 389 (M^+ − MOM, 8.92), 261 (11.36), 137 (23.23), 121 (100.00), 77 (5.07), 45 (25.20); HREIMS for $C_{23}H_{33}O_5$ (M-CH_3-OCH_2) calcd 389.2328, found 389.2352.

(8*S*,5′*S*)-8-Methoxymethoxy-10-(5′-methyl-2′-oxo-2′,5′-dihydrofuran-3′-yl)decanal (24). To a solution of **23** (0.085 g, 0.196 mmol) in CH_2Cl_2/H_2O (2.1 mL, v/v 20:1) at 0 °C was added DDQ (0.067 g, 0.294 mmol). The reaction mixture was stirred at room temperature for 1 h, diluted with ether, washed with saturated aqueous $NaHCO_3$ solution, and brine, and dried over Na_2SO_4. Concentration under reduced pressure and purification by column chromatography afforded an alcohol (0.045 g, 73%) as a light yellow oil: $[\alpha]_D$ +29.8 (*c* 0.41, $CHCl_3$); IR (film) 3450, 2933, 2858, 1754 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.03 (d, J = 1.6 Hz, 1H), 5.01 (qd, J = 6.9, 1.7 Hz, 1H), 4.68 (d, J = 6.9 Hz, 1H), 4.65 (d, J = 6.9 Hz, 1H), 3.64 (t, J = 6.6 Hz, 2H), 3.57 (m, 1H), 3.40 (s, 3H), 2.37 (m, 2H), 1.78 (m, 2H), 1.70 (m, 4H), 1.41 (d, J = 6.6 Hz, 3H), 1.33 (brs, 8H); EIMS (*m*/*z*) 297 (11.56), 283 (16.91), 253 (100.00), 235 (22.93), 199 (2.27), 169 (9.97).

A mixture of the above-obtained alcohol (0.040 g, 0.127 mmol) and Dess−Martin periodinane (0.081 g, 0.190 mmol) in CH_2Cl_2 (2 mL) was stirred at room temperature for 50 min, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography to afford aldehyde **24** (0.038 g, 96%) as a colorless oil: $[\alpha]_D$ +18.6 (*c* 0.13, $CHCl_3$); IR (film) 2934, 2858, 1755, 1712 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.78 (s, 1H), 7.03 (d, J = 1.7 Hz, 1H), 5.01 (qd, J = 6.9, 1.7 Hz, 1H), 4.68 (d, J = 6.9 Hz, 1H), 4.65 (d, J = 6.9 Hz, 1H), 3.58 (m, 1H), 3.40 (s, 3H), 2.44 (m, 2H), 2.37 (m, 2H), 1.79−1.46 (m, 4H), 1.42 (d, J = 6.6 Hz, 3H), 1.34 (brs, 8H); EIMS (*m*/*z*) 312 (M^+, 0.49), 297 (4.17), 283 (4.37), 267 (20.57), 249 (37.77), 199 (16.90), 169 (31.50), 112 (20.67), 45 (100.00).

(10′*EZ*,5*S*,3′S)-3-(11′-Iodo-3′-methoxymethoxyundec-10′-en-1′-yl)-5-methylfuran-2(5*H*)-one (5). To a suspension of $CrCl_2$ (0.081 g, 0.660 mmol) in THF (0.8 mL) at 0 °C was added a mixture of aldehyde **24** (0.034 g, 0.109 mmol) and iodoform (0.088 g, 0.224 mmol) in THF (2.5 mL). The reaction mixture was stirred at 0 °C for 5 h, quenched with H_2O, and extracted with ether. The extracts were washed with brine, dried, and concentrated. The residue was purified by column chromatography to afford **5** (0.035 g, 74%) as a 4:1 mixture of *E* and *Z* isomers in the form of an oil. $[\alpha]_D$ +37.2 (*c* 0.20, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.03 (d, J = 1.2 Hz, 1H), 6.52 (dt, J = 14.4, 7.2 Hz, 0.8 H from one olefinic proton of trans isomer), 6.18 (m, 0.4 H from two olefinic protons of cis isomer), 5.98 (dt, J = 14.4, 1.4 Hz, 0.8 H from one olefinic proton of trans isomer), 5.01 (qd, J = 6.6, 1.8 Hz, 1H), 4.67 (d, J = 7.2 Hz, 1H), 4.66 (d, J = 7.2 Hz, 1H), 3.57 (m, 1H), 3.40 (s, 3H), 2.42 (m, 1H), 2.33 (m, 1H), 2.15 and 2.06 (m and m, together 2 H), 1.81−1.70 (m, 2H), 1.59−1.48 (m, 2H), 1.42 (d, J = 6.6 Hz, 3H), 1.42−1.29 (m, 8H); EIMS (*m*/*z*) 391 (M^+-CH_3-OCH_2, 6.92), 375 (47.53), 247 (15.98), 199 (15.81), 167 (31.16), 169 (27.94), 45 (100.00).

MOM-Protected 6,7,12,13,14,14,15,15-Octadehydrotonkinecin (26). To a solution of **4** (0.081 g, 0.186 mmol) in Et_3N (8 mL) under N_2 were added $Pd(PPh_3)_2Cl_2$ (9.80 mg, 0.014 mmol) and CuI (7.00 mg, 0.037 mmol). The mixture was stirred at room temperature for 30 min, and to it was added a solution of **3** (0.078 g, 0.183 mmol) in Et_3N (2 mL). The reaction mixture was stirred at room temperature for 3 h and concentrated. The residue was purified by column chromatography to afford **26** (0.125 g, 93%) as an oil: $[\alpha]_D$ +55.8 (*c* 0.17, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.02 (d, J = 1.4 Hz, 1H), 6.03 (dt, J = 15.9, 7.1 Hz, 1H), 5.60 (dt, J = 10.7, 7.4 Hz, 1H), 5.42 (d, J = 15.8 Hz, 1H), 5.23 (m, 1H), 5.00 (m, 1H), 4.84 (d, J = 6.9 Hz, 1H), 4.77 (s, 2H), 4.67 (d, J = 6.9 Hz, 1H), 4.66 (d, J = 6.6 Hz,

1H), 4.48 (d, J = 6.6 Hz, 1H), 4.40 (m, 1H), 4.13 (m, 1H), 4.00 (m, 1H), 3.64 (q, J = 5.8 Hz, 1H), 3.47 (m, 1H), 3.41 (s, 3H), 3.39 (s, 3H), 3.36 (s, 3H), 2.65−2.22 (m, 3H), 2.13−1.55 (m, 11H), 1.41 (d, J = 6.9 Hz, 3H), 1.39 (m, 6H), 1.30−1.18 (m, 20H), 0.87 (t, J = 6.7 Hz, 3H); ESIMS (m/z) 756 ($M + Na^+$). Anal. Calcd for $C_{43}H_{72}O_9$: C, 70.48; H, 9.90. Found: C, 70.15; H, 10.32.

MOM-Protected 12,13,14,14,15,15-Hexadehydrotonkinecine (27). To a solution of **5** (0.035 g, 0.072 mmol) in Et_3N (3 mL) under N_2 were added $Pd(PPh_3)_2Cl_2$ (4.20 mg, 0.006 mmol) and CuI (3.10 mg, 0.016 mmol). The mixture was stirred at room temperature for 30 min, and to it was added a solution of **3** (0.036 g, 0.085 mmol) in Et_3N (2 mL). The reaction mixture was stirred at room temperature for 6 h and concentrated. The residue was purified by column chromatography to afford **27** (0.046 g, 86%) in the form of an oil: $[\alpha]_D$ +17.6 (c 0.18, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ7.02 (d, J = 1.2 Hz, 1H), 6.04, 5.81 and 5.43 (dt, J = 15.6, 7.2 Hz, dt, J = 10.0, 7.2 Hz and m, together 2H), 5.01 (qd, J = 6.6, 1.8 Hz, 1H), 4.84 (d, J = 6.6 Hz, 1H), 4.78 (s, 2H), 4.68 (d, J = 6.6 Hz, 1H), 4.67 (d, J = 6.6 Hz, 1H), 4.65 (d, J = 6.6 Hz, 1H), 4.15 (m, 1H), 4.02 (m, 1H), 3.65 (m, 1H), 3.57 (m, 1H), 3.48 (m, 1H), 3.42 (m, 1H), 3.402 (s, 3H), 3.395 (s, 3H), 2.63 (m, 1H), 2.53 (m, 1H), 2.40 (m, 1H), 2.34 (m, 1H), 2.07 (m, 2H), 2.02−1.94 (m, 2H), 1.82−1.26 (m and brs, 39H), 1.42 (d, J = 6.6 Hz, 3H); EIMS (m/z) 704 (4.27), 672 (9.07), 642 (15.07), 581 (12.38), 427 (11.99), 397 (20.24), 281 (22.08), 199 (9.00), 169 (11.30).

MOM-Protected Tonkinecin (28). To a mixture of enyne **26** (34 mg, 0.047 mmol) and *p*-toluenesulfony hydrazide (6.010 g, 32 mmol) in dimethoxyethane (6 mL) at reflux was added a solution of $NaOAc·H_2O$ in H_2O over a 2 h period. The reaction mixture was then cooled to room temperature and extracted with ether. The extracts were washed with brine and dried over Na_2SO_4. Removal of the solvent and purification by column chromatography afforded **28** (22 mg, 64%) as a colorless oil: $[\alpha]_D$ +46.6 (c 0.85, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.01 (s, 1H), 4.99 (qd, J = 6.6, 1.5 Hz, 1H), 4.83 (d, J = 6.6 Hz, 2H), 4.65 (m, 4H), 3.96 (m, 2H), 3.55 (m, 1H), 3.45 (m, 2H), 3.38 (s, 9H), 2.45−2.25 (m, 2H), 1.92 (m, 2H), 1.81−1.57 (m, 4H), 1.57−1.36 (m, 6H), 1.40 (d, J = 6.6 Hz, 3H), 1.24 (brs, 38), 0.87 (t, J = 6.2 Hz, 3H); EIMS (m/z) 597 (5.55), 585 (31.29), 573 (32.82), 555(84.89), 403 (42.15), 321 (71.94), 45 (100.00); ESIMS 764 (MNa^+). Anal. Calcd for $C_{43}H_{80}O_9$: C, 69.69; H, 10.88. Found: C, 69.56; H, 10.96.

In a similar procedure, 39 mg (0.053 mmol) of compound **27** and 0.682 g (3.64 mmol) of *p*-toluensulfony hydrazide afforded 26 mg (66%) of **28**.

Tonkinecin (1). To a solution of **28** (36 mg, 0.0486 mmol) in dimethyl sulfide (3 mL) at 0 °C was added $BF_3·Et_2O$ (0.5 mL). The reaction mixture was stirred at 0 °C for 1.5 h, quenched with saturated aqueous $NaHCO_3$ solution, and extracted with ether. The extracts were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography to afford **1** (26 mg, 86%) as a waxy solid: $[\alpha]_D$ +21.0 (c 0.57, $CHCl_3$) [lit.[4] $[\alpha]_D$ +26.54 (c 0.09, $CHCl_3$)]; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.03 (d, J = 1.2 Hz, 1H), 5.01 (dq, J = 1.2, 6.6 Hz, 1H), 3.81 (m, 2H), 3.60 (m, 1H), 3.41 (m, 2H), 2.46 (m, 1H), 2.38 (m, 1H), 1.99 (m, 2H), 1.76−1.60 (m, 4H), 1.54−1.37 (m, 6H), 1.41 (d, J = 6.6 Hz, 3H), 1.33−1.24(m, 38H), 0.88 (t, J = 6.6 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 174.10, 149.48, 134.08, 82.64, 77.57, 74.10, 70.93, 37.54, 35.40, 33.55, 31.94, 30.00−29.40 (br), 29.38, 28.80, 25.66, 22.71, 21.52, 19.19, 14.11; EIMS (m/z) 609, 391, 373, 339, 321, 155; ESIMS (m/z) 632 (MNa^+), 610 (MH^+), 592 ($MH^+ - H_2O$), 556 ($MH^+ - 3H_2O$);

Ethyl (4*S*)-4-Methoxymethoxy-5-oxo-pentanoate (34). Ester **33** (0.965 g, 3.49 mmol) was dissolved in 60% aqueous AcOH solution, stirred at 45 °C for 1 h, concentrated, and purified by column chromatography to give the product (0.629 g). The product was dissolved in 21 mL of CH_2Cl_2/H_2O (20:1, v/v), and to it was added sodium periodate (1.147 g, 5.36 mmol). The reaction mixture was stirred at room temperature for 1 h, and then Na_2SO_4 was added. After filtration and concentration, the residue was purified by column chromatography to afford aldehyde **34** (0.520 g, 73% for two steps) as an oil: $[\alpha]_D$ −35.2 (c 1.12, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.62 (d, J = 1.5 Hz, 1H), 4.72 (d, J = 7.0 Hz, 1H), 4.69 (d, J = 7.0 Hz, 1H), 4.12 (q, J = 7.1 Hz, 2H), 3.96 (m, 1H), 3.40 (s, 3H), 2.43 (t, J = 7.3 Hz, 2H), 2.12−1.88 (m, 2H), 1.24 (t, J = 7.1 Hz, 3H); EIMS (m/z) 205 (MH^+, 0.25), 173 ($M - CH_3O$, 14.01), 101 (2.87), 45 (100.00).

(2*R*)-6-Iodo-1,2-*O*-isopropylidenehexane-1,2-diol (38a). To a solution of alcohol **37** (1.540 g, 8.84 mmol) in CH_2Cl_2 (25 mL) at 0 °C were added triethylamine (2.5 mL), *p*-toluenesulfonyl chloride (3.362 g, 17.68 mmol), and DMAP (cat.). The reaction mixture was stirred at room temperature for 2 h, diluted with ether, washed with H_2O, saturated aqueous NH_4Cl solution, and brine, and dried over Na_2SO_4. The solvents were removed under reduced pressure, and the residue was purified by column chromatography to afford a tosylate (2.720, 94%) as a colorless oil: $[\alpha]_D$ −7.5 (c 1.1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.81 (d, J = 8.2 Hz, 2H), 7.35 (d, J = 8.2 Hz, 2H), 4.02 (m, 4H), 3.46 (m, 1H), 2.46 (s, 3H), 1.69 (m, 2H), 1.60−1.36 (m, 4H), 1.38 (s, 3H), 1.34 (s, 3H); EIMS (m/z) 173 (18.96), 155 (11.79), 107 (10.49), 91 (61.06), 85 (100.00).

The above tosylate (2.720 g, 8.28 mmol) was dissolved in acetone (60 mL), and to it were added sodium iodide (7.422 g, 49.48 mmol) and $NaHCO_3$ (2.064 g, 24.57 mmol). The reaction mixture was stirred at room temperature overnight. Most of the solvent was evaporated, and then to the residue was added ether. The mixture was washed with H_2O and brine, dried over Na_2SO_4, and concentrated. The crude product was purified by column chromatography to afford **38a** (2.310, 98%) as a colorless oil: $[\alpha]_D$ −8.9 (c 1.75, $CHCl_3$); IR (film) 2981, 2933, 2862, 1370 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.05 (m, 2H), 3.50 (m, 1H), 3.18 (t, J = 6.9 Hz, 2H), 1.85 (m, 2H), 1.70−1.32 (m, 4H), 1.40 (s, 3H), 1.34 (s, 3H); EIMS (m/z) 269 ($M^+ - CH_3$, 25.42), 127 (3.54), 101 (98.26), 43 (100.00). Anal. Calcd for $C_9H_{17}O_2I$: C, 38.04; H, 6.03. Found: C, 38.34; H, 6.18.

Ethyl (5*Z*,4*S*,10*R*)-10,11-Dihydroxy-10,11-*O*-isopropylidene-4-methoxymethoxy-5-undecenoate (39). To a solution of iodide **38a** (0.975 g, 3.43 mmol) in CH_3CN (25 mL) were added PPh_3 (1.798 g, 6.86 mmol) and $NaHCO_3$. The mixture was stirred at 85 °C for 12 h and concentrated under reduced pressure. To the residue was added CH_2Cl_2, and the mixture was filtered and concentrated. The obtained phosphonium salt was washed with ether several times, dried in vacuo, and dissolved in THF (30 mL). To it at 0 °C was added NaHMDS (3.5 mL, 1 M solution in THF, 3.5 mmol). After 30 min, the reaction mixture was cooled to −78 °C, and a solution of aldehyde **34** (0.520 g, 2.60 mmol) in THF (6 mL) was added. The reaction mixture was stirred at −78 °C for 2 h and quenched with brine, and the solvent was removed under reduced pressure. To the residue was added ethyl acetate, and the mixture was washed with ether and brine and dried over Na_2SO_4. Removal of the solvent and purification by column chromatography afforded **39** (0.707 g, 81%) as a colorless oil: $[\alpha]_D$ −87.0 (c 0.97, $CHCl_3$); IR (film) 2982, 2934, 1731, 1449, 1371 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.59 (dt, J = 10.4, 7.3 Hz, 1H), 5.22 (dd, J = 11.0, 9.2 Hz, 1H), 4.64 (d, J = 6.6 Hz, 1H), 4.46 (d, J = 6.6 Hz, 1H), 4.39 (m, 1H), 4.15−3.98 (m, 4H), 3.48 (m, 1H), 3.34 (s, 3H), 2.39 (t, J = 7.5 Hz, 2H), 2.11 (m, 2H), 1.95−1.30 (m, 6H), 1.39 (s, 3H), 1.33 (s, 3H), 1.24 (t, J = 7.1 Hz, 3H); EIMS (m/z) 329 ($M - CH_3$, 4.23), 101 (14.19), 45 (100.00). Anal. Calcd for $C_{18}H_{32}O_6$: C, 62.77; H, 9.36. Found: C, 62.73; H, 9.60.

Ethyl (4*R*,10*R*)-10,11-Dihydroxy-10,11-*O*-isopropylidene-4-methoxymethoxyundecanoate (40). A mixture of **39** (1.479 g, 3.42 mmol), 10% Pd/C (0.221 g), and $NaHCO_3$ in ethanol (25 mL) was stirred at room temperature for 4 h under 1 atm pressure of hydrogen, filtered through Celite, and washed with ethyl acetate. The filtrate was concentrated under reduced pressure and purified by column chromatography to afford **40** (1.440 g, 97%) as a colorless oil: $[\alpha]_D$ −18.9 (c 0.76, $CHCl_3$); IR (film) 2981, 2933, 1731, 1449, 1371 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.63 (s, 2H), 4.13 (q, J = 7.1 Hz, 2H), 4.03 (m, 2H), 3.56 (m, 1H), 3.49 (m, 1H), 3.37 (s, 3H), 2.38 (m, 2H), 1.86 (m, 1H), 1.76 (m, 1H), 1.71−1.30 (m, 10H), 1.40 (s, 3H), 1.35 (s, 3H), 1.25 (t, J = 7.1 Hz, 3H); EIMS (m/z) 331 ($M - CH_3$, 4.02), 175 (4.43), 101 (8.06), 45 (100.00).

Ethyl (4*R*,10*R*)-10,11-Dihydroxy-4-methoxymethoxyundecanoate (41a). Compound **40** (0.301 g, 0.87 mmol) was dissolved in 60% aqueous AcOH solution (4.5 mL). The mixture was stirred at 45 °C for 1 h and concentrated in vacuo. The crude product was purified by column chromatography to afford **41a** (0.260 g, 98%) a as an oil: $[\alpha]_D$ −10.33 (*c* 1.05, $CHCl_3$); IR (film) 3398, 2930, 1730, 1448, 1373 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.62 (s, 2H), 4.12 (q, J = 7.1 Hz, 2H), 3.68 (m, 2H), 3.55 (m, 1H), 3.42 (m, 2H), 3.36 (s, 3H), 2.37 (t, J = 7.4 Hz, 2H), 2.03 (br, 2H), 1.86 (m, 1H), 1.76 (m, 1H), 1.60−1.30 (m, 10H), 1.24 (t, J = 7.1 Hz, 3H); EIMS (*m*/*z*) 291 (M^+ − CH_3, 0.66), 175 (9.95), 45 (100.00). Anal. Calcd for $C_{15}H_{30}O_6$: C, 58.80; H, 9.87. Found: C, 58.94; H, 10.12.

Ethyl (4*R*,10*R*)-10-Hydroxy-4-methoxymethoxy-11-tosyloxyundecanoate (41b). To a stirred mixture of **41a** (0.140 g, 0.46 mmol) and dibutyltin oxide (0.023 g) in CH_2Cl_2 (1.5 mL) were added *p*-toluenesulfonyl chloride (0.091 g, 4.80 mmol) and triethylamine (67 uL). The reaction mixture was stirred at room temperature for 3 h, diluted with petroleum ether (3 mL), and chromatographed to afford **41b** (0.171 g, 81%) as an oil: $[\alpha]_D$ −13.0 (*c* 0.73, $CHCl_3$); IR (film) 3446, 2934, 1729, 1597, 1449, 1364 cm^{-1}; ^{1}HNMR (300 MHz, $CDCl_3$) δ 7.80 (d, J = 8.3 Hz, 2H), 7.36 (d, J = 7.9 Hz, 2H), 4.62 (s, 2H), 4.13 (q, J = 7.2 Hz, 2H), 4.03 (m, 1H), 3.90−3.78 (m, 2H), 3.52 (m, 1H), 3.37 (s, 3H), 2.46 (s, 3H), 2.38 (m, 2H), 1.95−1.68 (m, 2H), 1.55−1.30 (m, 10H), 1.25 (t, J = 7.2 Hz, 3H); EIMS (*m*/*z*) 443 [(M^+ − OH), 2.94], 181 (28.36), 155 (20.48), 91 (44.09), 45 (100.00). Anal. Calcd for $C_{22}H_{36}O_8S$: C, 57.37; H, 7.88. Found: C 57.45, H 7.69.

Ethyl (4*R*,10*R*)-10,11-Epoxy-4-methoxymethoxyundecanoate (6). A mixture of tosylate **41b** (0.306 g, 0.66 mmol) and DBU (0.2 mL) in CH_2Cl_2 (3 mL) was stirred at room temperature for 4 h, concentrated and purified by column chromatography to afford **6** (0.185 g, 97%) as a colorless oil: $[\alpha]_D$ −5.8 (*c* 1.07, $CHCl_3$); IR (film) 2934, 1731, 1100 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.63 (s, 2H), 4.13 (q, J = 7.1 Hz, 2H), 3.56 (m, 1H), 3.38 (s, 3H), 2.90 (m, 1H), 2.75 (dd, J = 5.0, 3.9 Hz, 1H), 2.46 (dd, J = 5.0, 2.8 Hz, 1H), 2.39 (m, 2H), 1.95−1.70 (m, 2H), 1.60−1.31 (m, 10H), 1.26 (t, J = 7.1 Hz, 3H); EIMS (*m*/*z*) 257 (M^+ − CH_3O, 1.22), 227 (M^+ − MOMO, 15.93), 175 (5.71), 45 (100.00). Anal. Calcd for $C_{15}H_{28}O_5$: C, 62.47; H, 9.79. Found: C, 62.45; H, 9.67.

Ethyl (4*R*,10*R*,15*R*,2′*R*,5′*R*,1″*R*)-4,15-Bis(methoxymethoxy)-15-[5′-(1″-methoxymethoxytridec-1″-yl)tetrahydrofuran-2′-yl]-10-hydroxy-12-pentadecynoate (42). To a stirred solution of alkyne **3** (72 mg, 0.17 mmol) in THF (1 mL) at −78 °C was added a solution of BuLi (2.5 M solution in hexane, 67.5 μL, 0.17 mmol). After 1 h, $BF_3{\cdot}Et_2O$ (21.0 μL, 0.23 mmol) was added. The mixture was stirred for 40 min, and a solution of epoxide **6** (60 mg, 0.21 mmol) in THF (0.7 mL) was added. The reaction mixture was stirred at −78 °C for 2 h, quenched with saturated aqueous NH_4Cl solution, and extracted with ether. The extracts were washed with brine, dried, and concentrated. The residue was purified by column chromatography to afford **42** (93 mg, 77%) as a colorless oil: $[\alpha]_D$ + 3.5 (*c* 0.79, $CHCl_3$); IR (film) 3462, 2925, 2852, 1731 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 4.88 (d, J = 6.6 Hz, 1H), 4.78 (d, J = 6.6 Hz, 1H), 4.74 (d, J = 6.6 Hz, 1H), 4.66 (d, J = 6.6 Hz, 1H), 4.64 (d, J = 6.6 Hz, 1H), 4.62 (d, J = 6.6 Hz, 1H), 4.13 (q, J = 7.2 Hz, 2H), 4.13 (m, 1H), 4.01 (m, 1H), 3.67 (m, 1H), 3.64 (q, J = 7.0 Hz, 1H), 3.56 (m, 1H), 3.46 (m, 1H), 3.41 (s, 3H), 3.40 (s, 3H), 3.37 (s, 3H), 2.52 (m, 1H), 2.45−2.34 (m, 4H), 2.23 (ddd, J = 14.4, 7.8, 2.4 Hz, 1H), 1.96 (m, 2H), 1.88 (m, 1H), 1.76 (m, 2H), 1.66 (m, 1H), 1.57−1.21 (m, 35H), 0.88 (t, J = 6.9 Hz, 3H); EIMS (*m*/*z*) 590 (3.39), 559 (4.34), 213 (24.26), 45 (100.00); ESIMS 738 (MNa^+). Anal. Calcd for $C_{40}H_{74}O_{10}$: C, 67.19; H, 10.43. Found: C, 67.42; H, 10.28.

Ethyl (4*R*,10*R*,15*R*,2′*R*,5′*R*,1″*R*)-4,15-Bis(methoxymethoxy)-15-[5′-(1″-methoxymethoxy-tridec-1″-yl)tetrahydrofuran-2′-yl]-10-hydroxypentadecanoate (43a). A mixture of **42** (0.210 g, 0.29 mmol) and PtO_2 (8 mg) in ethanol (4 mL) was stirred at room temperature for 3 h under 1 atm pressure of hydrogen and filtered. The filtrate was concentrated and purified by column chromatography to afford **43a** (0.195 g, 92%) as a colorless oil: $[\alpha]_D$ +29.5 (*c* 0.77, $CHCl_3$); IR (film) 3478, 2925, 2853, 1731, 1460, 1371 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.84 (d, J = 6.6 Hz, 2H), 4.67 (d, J = 6.6 Hz, 2H), 4.63 (s, 2H), 4.13 (q, J = 7.1 Hz, 2H), 3.98 (m, 2H), 3.56 (m, 2H), 3.47 (m, 2H), 3.39 (s, 6H), 3.38 (s, 3H), 2.39 (m, 2H), 1.96−1.22 (m, 49H), 0.88 (t, J = 6.8 Hz, 3H); ESIMS 742 (MNa^+).

Ethyl (4*R*,10*R*,15*R*,2′*R*,5′*R*,1″*R*)-4,10,15-Tris(methoxymethoxy)-15-[5′-(1″-methoxymethoxytridec-1″-yl)tetrahydrofuran-2′-yl]pentadecanoate (43b). To a mixture of alcohol **43a** (0.172 g, 0.24 mmol) and diisopropylethylamine (0.82 mL, 4.70 mmol) in CH_2Cl_2 (3.7 mL) at 0 °C was added MOMCl (0.27 mL, 3.55 mmol). The mixture was stirred at room temperature for 5 h, diluted with ether, washed with H_2O and brine, and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the residue was purified by column chromatography to afford **43b** (0.174 g, 95%) as a colorless oil: $[\alpha]_D$ +26.30 (*c* 1.23, $CHCl_3$); IR (film) 2925, 2853, 1734 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.83 (d, J = 6.6 Hz, 2H), 4.66 (d, J = 6.6 Hz, 2H), 4.635 (s, 2H), 4.631 (s, 2H), 4.13 (q, J = 7.1 Hz, 2H), 3.98 (m, 2H), 3.60−3.42 (m, 4H), 3.39 (s, 6H), 3.373 (s, 3H), 3.368 (s, 3H), 2.39 (m, 2H), 1.97−1.58 (m, 6H), 1.56−1.22 (m, 43H), 0.88 (t, J = 6.7 Hz, 3H); EIMS (*m*/*z*) 626 (1.83), 594 (8.24), 564 (12.4), 281 (13.69), 45 (100.00). Anal. Calcd for $C_{42}H_{82}O_{11}$: C, 66.11; H, 10.83. Found: C, 66.44; H, 10.80.

MOM-Protected Annonacin (44). To a solution of diisopropylamine (0.13 mL, 0.92 mmol) in THF (1.6 mL) at 0 °C was added BuLi (0.23 mL, 2.5 M solution in THF, 0.58 mmol). The mixture was stirred at 0 °C for 10 min and then cooled to −78 °C, and a solution of ester **42b** (0.172 g, 0.23 mmol) in THF (1.7 mL) was added. After 60 min, a solution of aldehyde **13** (0.080 g, 0.51 mmol) in THF (1 mL) was added. The reaction was stirred at −78 °C for 2 h, quenched with saturated aqueous NH_4Cl solution, and extracted with ether. The extracts were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified with column chromatography to afford aldol product (0.205 g, 98%) as a mixture of diastereoisomers: IR (film) 3461, 2925, 1728, 1466, 1376 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.83 (d, J = 6.6 Hz, 2H) 4.70−4.56 (m, 7H), 4.12 (m, 3H), 3.97 (m, 2H), 3.92−3.52 (m, 3H), 3.47 (m, 4H), 3.39,3.37 (2s, 12H), 2.63 (m, 1H), 2.02−1l.15 (m, 58H), 0.88 (t, J = 6.6 Hz, 3H); ESIMS 944 (MNa^+).

The above-obtained mixture (0.200 g, 0.22 mmol) was dissolved in AcOH/THF/H_2O (10 mL, 4:2:1). The reaction mixture was stirred at 45 °C for 5 h and concentrated in vacuo. To a mixture of the residue (0.195 g) and triethylamine (0.34 mL, 2.42 mmol) in CH_2Cl_2 (9.5 mL) at 0 °C was added trifluoroacetic anhydride (0.20 mL, 1.41 mmol). The reaction mixture was stirred at room temperature for 20 h, diluted with ether and washed with saturated aqueous $NaHCO_3$ solution and brine, dried over Na_2SO_4. Removal of the solvent gave crude product which, after chromatography, afforded **44** (0.076 g, 45%) as a colorless oil: $[\alpha]_D$ +38.0 (*c* 0.8, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.16 (s, 1H), 5.02 (m, 1H), 4.84 (d, J = 6.6 Hz, 2H), 4.70−4.61 (m, 6H), 3.97 (m, 2H), 3.82 (m, 1H), 3.58−3.35 (m, 3H), 3.39 (s, 6H), 3.37 (s, 3H), 3.34 (s, 3H), 2.51 (m, 1H), 2.49 (m, 1H), 1.93 (m, 2H), 1.78−1.20 (m, 45H), 1.39 (d, J = 8.0 Hz, 3H), 0.88 (t, J = 6.6 Hz, 3H); ESIMS 796 (MNa^+).

Annonacin (2). To a solution of **62** (66 mg, 0.085 mmol) in dimethyl sulfide (7.2 mL) at 0 °C was added $BF_3{\cdot}Et_2O$ (1.1 mL). The reaction mixture was stirred room temperature for 40 min, cooled to 0 °C, quenched with saturated aqueous $NaHCO_3$ solution, and extracted with ethyl acetate. The extracts were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography to afford **2** (44 mg, 86%) as a white solid: mp 69−71 °C; $[\alpha]_D$ +21 (*c* 0.51, $CHCl_3$) [lit.[17] $[\alpha]_D$ +20.78 (*c* 5.05 $CHCl_3$)]; $[\alpha]_D$ +19 (*c* 0.40, CH_3OH) [lit.[18] $[\alpha]_D$ = 11.4 (c 0.04 CH_3OH)]; ^1H NMR (600 MHz, $CDCl_3$) δ 7.18 (s, 1H), 5.06

(17) Zhang, L.-L.; Yang, R.-Z.; Wu, S.-J. *Acta Botanica Sinica (Zhiwu Xuebao)* **1993**, *35*, 390.

(18) Chen, W.-S.; Yao, Z.-J.; Wu, Y.-L. *Youji Huaxue* **1995**, *15*, 85.

(q, J = 6.6 Hz, 1H), 3.85 (m, 1H), 3.81 (dt, J = 11.7, 6.6 Hz, 2H), 3.59 (m, 1H), 3.41 (dt, J = 11.7, 6.0 Hz, 2H), 2.52 (d, J = 14.7 Hz, 1H), 2.40 (dd, J = 14.7, 7.8 Hz, 1H), 2.04 (br. 4 OH), 1.99 (m, 2H), 1.68 (m, 2H), 1.60−1.20 (m, 40H), 1.43 (d, J = 7.2 Hz, 3H), 0.88 (t, 6.8 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 174.58, 151.80, 131.18, 82.67, 82.60, 77.95, 74.05, 73.95, 71.74, 69.90, 37.36, 37.27, 33.48, 33.37, 29.70−29.57 signal overlap, 29.47, 29.32, 28.72, 25.64, 25.58, 25.48, 22.66, 19.09, 14.08.

Acknowledgment. This research was supported by the State Ministry of Science and Technology of China (970211006-6), Chinese Academy of Sciences (KJ-951-A1-504-04, KJ-952-S1-503), the National Natural Science Foundation of China (29472070, 29790126), and the Major State Basic Research Development Program (G2000077502). We are grateful to Professor D. Q. Yu, Institute of Material Medical, Chinese Academy of Medical Sciences, for comparing the spectra of **1** with those of the natural product.

Supporting Information Available: Experimental details for compounds **8**−**10**, **12a**,**b**, **30**−**33**, **36**, and **37**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO005643B