Enantioselective Total Synthesis of (+)-Gigantecin: Exploiting the Asymmetric Glycolate Aldol Reaction

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Plants of the family Annonaceae produce an abundant collection of highly bioactive C35−C37 fatty acid metabolites.[1] These acetogenins have been found to effect potent depletion of ATP levels via inhibition of complex I (NADH, ubiquinone oxidoreductase) of mammalian and insect mitochondrial transport systems and inhibition of the NADH oxidase of plasma membranes of tumor cells.[2] Consequently, they disrupt ATP-driven resistance mechanisms and have shown activity against multidrug-resistant tumor types.[3] The three main classes of annonaceous acetogenins are monotetrahydrofuran, adjacent bis-THF, and nonadjacent bis-THF subclasses. The significant biological activity of the acetogenins, as well as their interesting and diverse structures, has stimulated substantial interest in their chemical synthesis.[4] Gigantecin (**1**), a representative nonadjacent bis-THF acetogenin, was isolated from the bark of *Goniothalamus giganteus* in Southeast Asia[5] and the seed of the Brazilian plant *Annona coriacea*.[6] The relative and absolute configurations of gigantecin were assigned after extensive spectroscopic and Mosher ester analysis, and the assignment was confirmed by single-crystal X-ray analysis.[5,6] Gigantecin displayed potent cytotoxicity against A-549 (lung carcinoma), HT-29 (colon adenocarcinoma), MCF-7 (breast adenocarcinoma), and U251MG (glioblastoma multiforme) human tumor cell lines at ED_{50}s of 0.4, 0.001, 4.3, and 0.003 µg/mL, respectively.[5]

Herein we disclose the first total synthesis of (+)-gigantecin.[7] The synthesis exploits a modified asymmetric aldol protocol using chlorotitanium enolates of oxazolidinone glycolates. Strategically, gigantecin was envisioned to derive from a convergent assembly of three key subunits (Figure 1). The confluence of acetylene **4** and aldehyde **5** according to Carreira's[8] method would join the two tetrahydrofuran rings and establish the C17 stereocenter. Conversion of the acetylide adduct to acetylene **3** would set the stage for its coupling[9] to butenolide **2** leading to completion of the synthesis. Both acetylene **4** and aldehyde **5** would be accessible by applying an asymmetric glycolate aldol−ring-closing metathesis sequence. The C1−C6 butenolide **2** was constructed as shown in Scheme 1. Alkylation of the sodium enolate of oxazolidinone glycolate **6** with allylic iodide **7** proceeded in good yield (71%) and excellent diastereoselectivity (>98:2).[10] The chiral auxiliary was reductively cleaved, and the ensuing primary alcohol was protected as its TBDPS ether to deliver vinyl bromide **9**. Lithium−halogen exchange of bromide **9** and reaction with CO_2 produced the acrylic acid derivative, which cleanly gave ester **11** upon inversion of alcohol **10** under Mitsunobu conditions.[11] Diene **11** was exposed to the Grubbs second-generation catalyst[12] to produce butenolide **12** in 95% yield. Removal of the silyl ether of **12** furnished primary alcohol **13**. Alcohol **13** was oxidized to aldehyde, which underwent Takai olefination[13] to give the required vinyl iodide **2**.

The syntheses of both the C9−C16 alkyne **4** and the C17−C34 aldehyde **5** were predicated on the implementation of a newly developed protocol for asymmetric aldol reactions of complex glycolyl oxazolidinone chlorotitanium enolates.[14] Glycolate **15** was
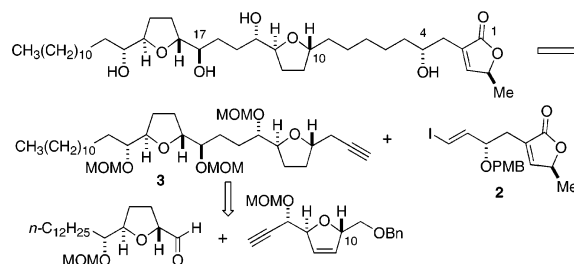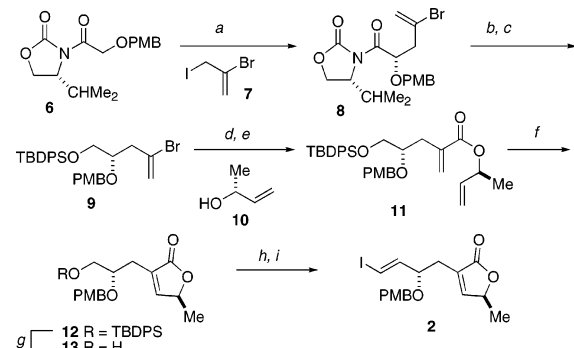

Figure 1. Retrosynthesis of (+)-gigantecin.

Scheme 1. Synthesis of Butenolide **2**[a]

[a] Conditions: (a) NaN(SiMe₃)₂, THF, −78 to −45 °C, iodide **7**, 71%; (b) NaBH₄, THF, H₂O, 92%; (c) TBDPSCl, imidazole, CH₂Cl₂, 72%; (d) *t*-BuLi, THF, −78 °C; CO₂, 82%; (e) DEAD, Ph₃P, THF, alcohol **10**, 87%; (f) Cl₂(Cy₃P)(IMes)Ru=CHPh, CH₂Cl₂, 40 °C, 95%; (g) 3HF−Et₃N, CH₃CN, 94%; (h) (COCl)₂, DMSO, Et₃N, CH₂Cl₂, 97%; (i) CHI₃, CrCl₂, THF, 62% (two steps).

Scheme 2. Synthesis of C9−C16 Fragment **4**[a]
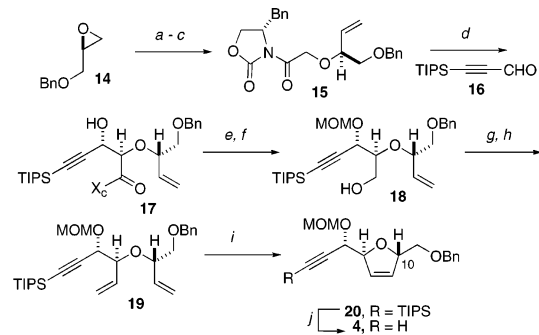
[a] Conditions: (a) Me₃SI, *n*-BuLi, THF, −10 to 25 °C, 99%;[16] (b) NaH, BrCH₂CO₂H, THF, 98%; (c) Me₃CCOCl, Et₃N, THF, −78 to 0 °C; (*R*)-lithio-4-benzyl-oxazolidin-2-one, 78%; (d) TiCl₄, *i*-Pr₂NEt, *N*-methyl-2-pyrrolidinone, aldehyde **16**, CH₂Cl₂, −78 to −40 °C, 93%; (e) MeOCH₂Cl, *i*-Pr₂NEt, CH₂Cl₂, DMAP, 91%; (f) LiBH₄, MeOH, Et₂O, 0 °C, 92%; (g) (COCl)₂, DMSO, Et₃N, CH₂Cl₂; (h) Ph₃P=CH₂, THF, 91%, two steps; (i) Cl₂(Cy₃P)(IMes)Ru=CHPh, CH₂Cl₂, 40 °C, 99%; (j) *n*-Bu₄NF, THF, 98%.

prepared in three straightforward steps from (*S*)-benzyl glycidyl ether **14** as shown in Scheme 2. Glycolate **15** was treated with TiCl₄ (1.05 equiv) and *i*-Pr₂NEt (2.5 equiv) for 1 h at −78 °C followed by *N*-methyl-2-pyrrolidinone (1.0 equiv) at −78 °C for 10 min. Aldehyde **16** was added to the enolate followed by warming to −40 °C. This procedure resulted in a highly diastereoselective aldol

Scheme 3. Synthesis of C17−C34 Fragment **5**[a]
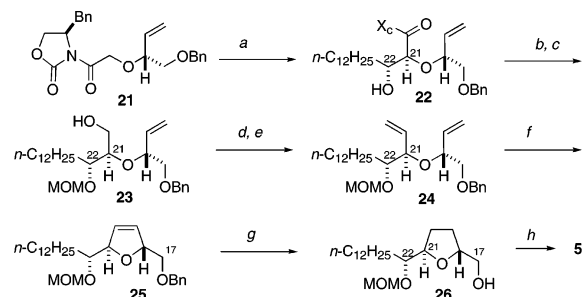
[a] Conditions: (a) TiCl₄, *i*-Pr₂NEt, *N*-methyl-2-pyrrolidinone, tridecanal, CH₂Cl₂, −78 to −40 °C, 74%; (b) MeOCH₂Cl, *i*-Pr₂NEt, CH₂Cl₂, DMAP, 91%; (c) LiBH₄, MeOH, Et₂O, 0 °C, 95%; (d) (COCl)₂, DMSO, Et₃N, CH₂Cl₂; (e) Ph₃P=CH₂, THF, 90%, two steps; (f) Cl₂(Cy₃P)(IMes)Ru=CHPh, CH₂Cl₂, 40 °C, 99%; (g) H₂, Pd/C, EtOH, 83%; (h) (COCl)₂, DMSO, Et₃N, CH₂Cl₂.

reaction to deliver the alcohol **17** in 93% yield and >20:1 dr (major: all other isomers). Protection of the secondary alcohol as its MOM ether and reductive removal of the auxiliary afforded the alcohol **18**. The primary alcohol **18** was oxidized under Swern conditions,[15] and the aldehyde was immediately converted to the alkene **19**. Exposure of diene **19** to the Grubbs second-generation catalyst[12] led to selective formation of the dihydrofuran **20** in high yield with no indication of reaction of the acetylene. The terminal TIPS group was readily removed leading to the desired alkyne **4**.

The C17−C34 aldehyde **5** was similarly constructed as illustrated in Scheme 3. Once again, the NMP-promoted asymmetric aldol reaction was exploited, in this instance to establish the C21 and C22 stereogenic centers. The alcohol **22** was obtained in 74% yield (>15:1 dr) upon exposure of glycolate **21** (*ent*-**15**) to aldol conditions identical to those described above with the exception of utilizing tridecanal as the aldehyde component. Protection of the secondary alcohol as its MOM ether followed by reduction of the glycolate carbonyl gave the alcohol **23**. Oxidation of the alcohol and olefination of the derived aldehyde provided the diene **24**. The diene **24** was subjected to the Grubbs catalyst[12] as before, resulting in formation of the dihydrofuran **25**. Exposure of dihydrofuran **25** to hydrogen in the presence of Pd/C effected concomitant reduction of the alkene and hydrogenolysis of the C17 benzyl ether to give **26**. The C17 alcohol **26** was then converted to the aldehyde **5** under Swern conditions.[15]

With the three required fragments in hand, their assembly to (+)-gigantecin was undertaken. The Carreira method for asymmetric acetylide[8] addition was chosen for the addition of acetylene **4** to aldehyde **5** since others had noted low diastereoselectivity in similar additions without chiral additives.[17] In the event, addition of acetylene **4** to Zn(OTf)₂ and (−)-*N*-methylephedrine in toluene followed by addition of aldehyde **5** produced the propargylic alcohol **27** in 70% yield (two steps including Swern oxidation) as a single detectable stereoisomer (Scheme 4). The C17 hydroxyl was protected as its MOM ether to deliver **28**. Treatment of enyne **27** with hydrogen in the presence of Pd/C led to the concomitant reduction of the double and triple bonds as well as removal of the C9 benzyl ether to give alcohol **29**. Formation of the C9 triflate with its ensuing displacement by lithium trimethylsilylacetylide provided the acetylene **3** in high yield. The final C−C bond was fashioned by palladium-mediated coupling[9] of the acetylene **3** with vinyl iodide **2** to provide enyne **30**. Selective hydrogenation[4d] of the C5−C8 enyne followed by removal[4d] of the protecting groups led to the

Scheme 4. Synthesis of (+)-Gigantecin[a]
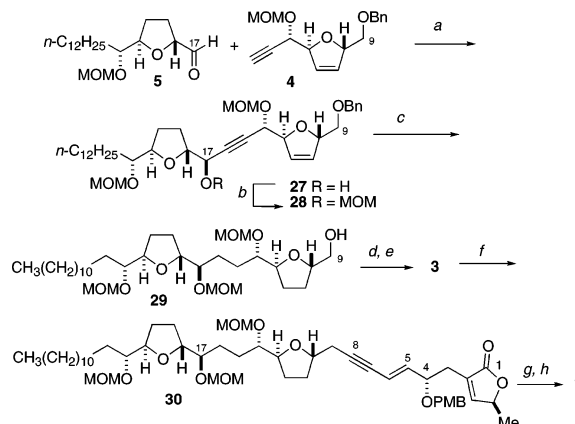
[a] Conditions: (a) Zn(OTf)₂, (−)-*N*-methylephedrine, PhCH₃, **4** then **5**, 70% for two steps from **26**; (b) MeOCH₂Cl, *i*-Pr₂NEt, CH₂Cl₂, DMAP, 97%; (c) H₂, Pd/C, EtOH, 97%; (d) Tf₂O, Et₃N, CH₂Cl₂ −78 °C; (e) Me₃SiC≡CH, *n*-BuLi, THF, HMPA, −78 °C; MeOH, 25 °C, 95% for two steps; (f) iodide **2**, Pd(PPh₃)₄, CuI, *i*-Pr₂NEt, THF, 64%; (g) H₂, Rh(PPh₃)₃Cl, C₆H₆, EtOH, LiI 61%; (h) BF₃·OEt₂, Me₂S, 0 °C, 71%.

completion of the synthesis of (+)-gigantecin. Synthetic gigantecin was identical (¹H, ¹³C NMR, [α]²⁴_D) to the natural material.

The first total synthesis of the annonaceous acetogenin (+)-gigantecin has been completed in an enantioselective manner in 19 linear steps from commercially available benzyl glycidyl ether.

Supporting Information Available: Experimental procedures as well as ¹H and ¹³C NMR spectra for all new compounds and synthetic (+)-gigantecin (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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