Pergamon

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TETRAHEDRON: *ASYMMETRY*

A facile route to the total synthesis of gigantetrocin A

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Abstract

A highly efficient synthetic method of the *trans*-mono-tetrahydrofuran (THF) ring building block was established and the title compound synthesized in 19 steps from *trans*-1,4-dichloro-2-butene via a convergent route with a Wittig reaction as the key step.

In recent years, the rapidly growing class of naturally occurring Annonaceous acetogenins has received considerable attention, due to their broad spectrum of biological activities such as cytotoxic, antitumor, antimicrobial, antimalarial, antifeedant, pesticidal and immunosuppressive effects.[1] Gigantetrocin A was isolated by McLaughlin's group from *Goniothalamus giganteus* Hook. f. and Thomas (Annonaceae)[2] and showed significant and selective cytotoxicity to human tumor cells in culture.[2,3] Its absolute configuration has been determined by spectroscopic analysis. The striking characteristics are the existence of four hydroxyl groups, an α,β-unsaturated γ-lactone and a mono *trans*-tetrahydrofuran (THF) ring unit (Fig. 1).

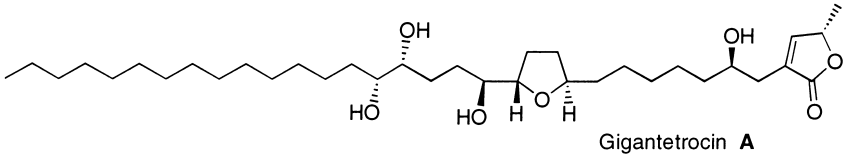

Figure 1.

Although its diasteromer (+)-densicomacin has been synthesized by Cassady's group,[4] no successful synthesis of this interesting natural product has been achieved to date. Herein we wish to report our facile route to the first total synthesis of gigantetrocin A.

A Sharpless AD reaction[5] on *trans*-1,4-dichloro-2-butene **1** installed the two primitive obtained stereogenic centers, with greater than 94% ee,[6] in the mono-THF ring backbone. The diol **2** was subsequently treated with NaH and allylmagnesium chloride in the presence of CuI to produce another diol **3** in 79% yield which was mono-protected by MOMCl and then oxidatively cyclized to form a mono

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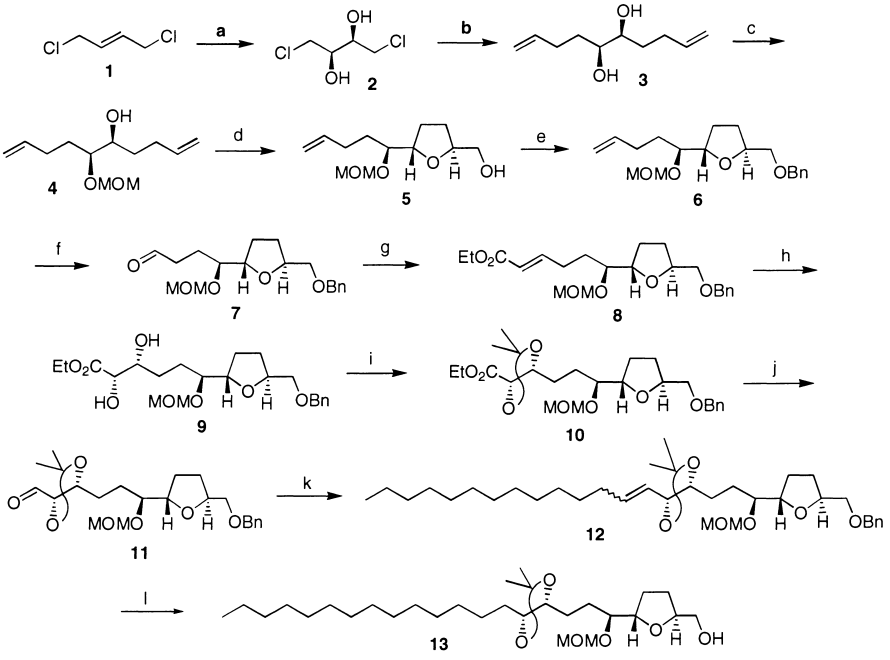
trans-THF ring compound **5** with greater than 95% de[7] in 78% yield using $Co(modp)_2$[8] as a catalyst under an oxygen atmosphere. Protection of **5** gave benzyl ether **6** which was dihydroxylated and underwent an oxidative cleavage reaction to afford aldehyde **7**. The Horner–Emmons reaction on **7** gave **8**, and diol **9** was obtained by the use of a further Sharpless AD reaction. After protection of the diol group by isopropylidene ketal, aldehyde **11** was produced by reduction with $LiAlH_4$ and Swern oxidation which then reacted with Wittig salt $CH_3(CH_2)_{12}P^+Ph_3Br^-$ in the presence of BuLi in THF to give **12** (*E*-isomer predominated). The catalytic hydrogenation over Pd/C gave segment **13** in 83% yield (Scheme 1).

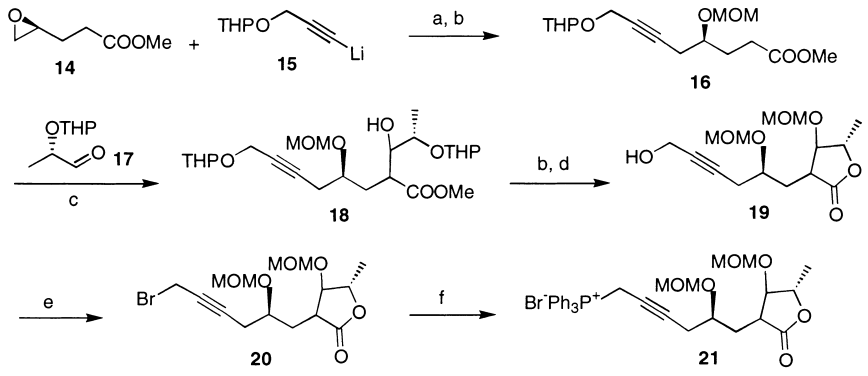


Conditions: a) $K_3Fe(CN)_6$, K_2CO_3, $NaHCO_3$, $MeSO_2NH_2$, $(DHQ)_2PHAL$, $K_2OsO_2(OH)_4$, ^tBuOH: H_2O (1:1), 0 °C; 84%. b) 1) NaH, THF; 2) allylmagnesium chloride, CuI, THF, -50°C; 79%. c) NaH, MOMCl, THF; 67%. d) $Co(modp)_2$, TBHP, O_2, *i*-PrOH; 74%. e) NaH, BnBr, THF; 98%. f) 1) $K_3Fe(CN)_6$, K_2CO_3, $K_2OsO_2(OH)_4$, ^tBuOH:H_2O (1:1), rt; 2) $NaIO_4$, THF:H_2O (1:1). g) $Ph_3P{=}CHCO_2Et$, PhH; 90% (three steps). h) $K_3Fe(CN)_6$, K_2CO_3, $(DHQD)_2PHAL$, $K_2OsO_2(OH)_4$, ^tBuOH:H_2O (1:1), 0 °C; 97%. i) $Me_2C(OMe)_2$, PPTS. j) 1) $LiAlH_4$, Et_2O; 2) Swern oxidation. k) $CH_3(CH_2)_{12}P^+Ph_3\ Br^-$, BuLi, THF, -78-0°C; 34% (4 steps). l) Pd/C, H_2, EtOH, 83%.

Scheme 1.

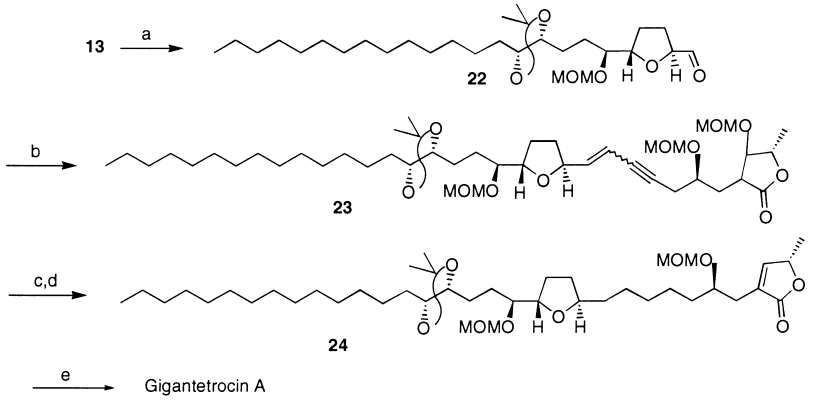
Preparation of segment **21** is shown in Scheme 2. Epoxide **14**[9] was opened by lithium alkynylide **15** in the presence of $BF_3\cdot OEt_2$ and the resulting alcohol was treated with MOMCl/*i*-Pr_2NEt to give **16**. Aldol condensation of the enolate for **16** and aldehyde **17**[10] produced compound **18**. Protection of the newly generated hydroxyl group in **18** as a MOM ether and treatment with 9% H_2SO_4:THF (1:3) afforded lactone **19**.[10] Bromination of the propargyl alcohol **19** gave segment **20**, which was then reacted with PPh_3 to afford the Wittig salt **21**.

The coupling reaction between aldehyde **22**, prepared from **13** in situ by Swern oxidation, and the ylide prepared from **21** gave enyne **23** (*Z*-isomer predominated) in 28% yield which was hydrogenated over Wilkinson's catalyst and then treated with DBU to afford **24**[11] in 69% yield (Scheme 3). Deprotection of **24** by $BF_3\cdot OEt_2$ gave the target compound in 59% yield which has a very close specific rotation {$[\alpha]_D^{20}$ +13.1 (c 0.35, $CHCl_3$); lit.[3] $[\alpha]_D^{20}$ +14.3 (c 0.45, $CHCl_3$)} and the same spectral data as those reported in other literature.[2,3]



Conditions: a) $BF_3{\cdot}OEt_2$, THF, -78 °C; 83%. b) MOMCl, *i*-Pr_2NEt, CH_2Cl_2; 86%. c) LDA, THF, -78 °C; then **17**; 80%. d) 9% H_2SO_4, THF; 65% (two steps). e) PPh_3, CBr_4, CH_2Cl_2; 89%. f) PPh_3, PhH, 87%.

Scheme 2.



Conditions: a) Swern oxidation. b) **21**, ^{t}BuOK, THF, -78 °C; 28% (two steps). c) $(PPh_3)_3RhCl$, H_2, EtOH. d) DBU, THF; 69% (two steps). e) $BF_3{\cdot}OEt_2$, DMS; 59%.

Scheme 3.

In conclusion, we have developed an efficient procedure for the stereocontrolled synthesis of the THF ring unit and a convenient route for coupling this key intermediate with other building blocks. The first total synthesis of gigantetrocin A has been achieved in 19 steps from *trans*-1,4-dichloro-2-butene (**1**).

Acknowledgements

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6. The ee of the resulting diol **2** {$[\alpha]_D^{20}$ +11.6 (c 1.70, CH_2Cl_2)} is determined by comparing the specific optical rotation with its opposite enantiomer {$[\alpha]_D^{19}$ −11.1 (c 2.75, CH_2Cl_2); lit. $[\alpha]_D$ −11.7 (c 1.5, CH_2Cl_2)} reported in literature (Vanhessche, K. P. M.; Wang, Z.-M.; Sharpless, K. B. *Tetrahedron Lett*. **1994**, *35*, 3469).
7. No *cis*-THF ring was formed in this step based on the ^{1}H NMR ($CDCl_3$, 300 MHz) and ^{13}C NMR ($CDCl_3$, 75 MHz) spectral analysis. Physical data for compound **5**: colorless oil; $[\alpha]_D^{20}$ −24.1 (c 1.58, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.50–1.76 (m, 4H), 1.89–2.03 (m, 2H), 2.08–2.27 (m, 2H), 3.41 (s, 3H), 3.46–3.55 (m, 2H), 3.62–3.68 (m, 1H), 3.99–4.13 (m, 2H), 4.70 (d, *J*=6.8 Hz, 1H), 4.81 (d, *J*=6.8 Hz, 1H), 4.98 (dm, *J*=10.2 Hz, 1H), 5.04 (dm, *J*=17.1 Hz, 1H), 5.82 (ddt, *J*=17.1, 10.2, 6.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 27.56, 28.49, 29.62, 30.54, 55.83, 64.79, 79.42, 79.61, 81.37, 96.92, 114.84, 138.45; EIMS: m/z 229 (M−H, 0.63), 215 (0.76), 199 (100); IR (neat): ν 3426, 1639 cm^{-1}. HRMS calcd for $C_{12}H_{22}O_4$: 230.1518; Found: 230.1521.
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11. The spectral data of this compound: colorless oil; $[\alpha]_D^{20}$ −1.0 (c 0.50, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.88 (3H, t, *J*=6.8 Hz), 1.20–1.37 (30H, m), 1.37–1.82 (10H, m), 1.38 (6H, s), 1.41 (3H, d, *J*=7.1 Hz), 1.91–2.08 (2H, m), 2.50 (2H, d, *J*=5.8 Hz), 3.35–3.44 (6H, m), 3.46–3.66 (3H, m), 3.79–4.05 (3H, m), 4.60–4.75 (3H, m), 4.84 (1H, d, *J*=6.9 Hz), 4.95–5.05 (1H, m), 7.16–7.18 (1H, m); EIMS: m/z 525 (6), 450 (13), 432 (5); IR (neat): ν 2921, 1756 cm^{-1}.