Pergamon

Tetrahedron Letters, Vol. 38, No. 25, pp. 4437-4440, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)00925-8

An Asymmetric Total Synthesis of (-)-Fumagillol

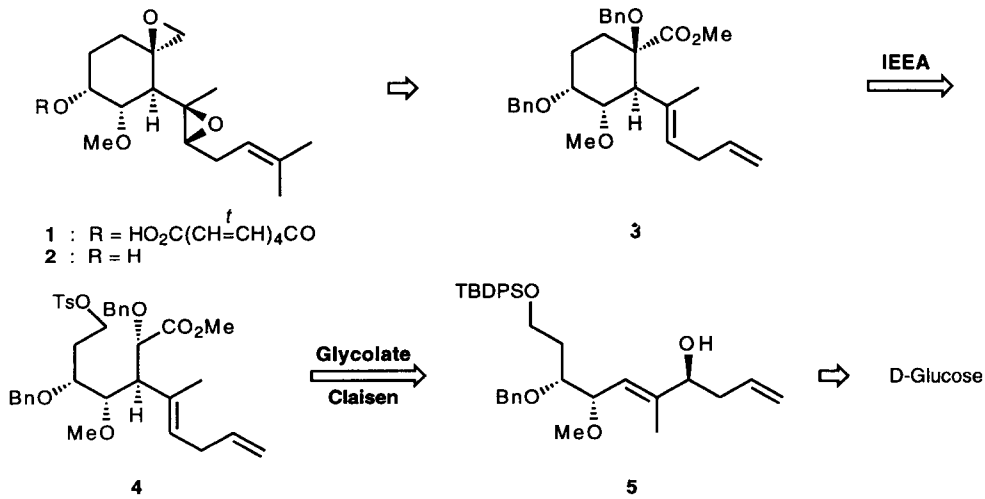
Deukjoon Kim*, Soon Kil Ahn, Hoon Bae, Won Jun Choi, and Hak Sung Kim

College of Pharmacy, Seoul National University, San 56-1, Shinrim-Dong, Kwanak-Ku, Seoul 151-742, Korea

Abstract: (-)-Fumagillol (**2**), a hydrolysis product of fumagillin (**1**), has been synthesized in a highly stereoselective manner utilizing a glycolate Claisen rearrangement and an intramolecular ester enolate alkylation as key steps starting from carbohydrate-based precursor **5**. © 1997 Elsevier Science Ltd.

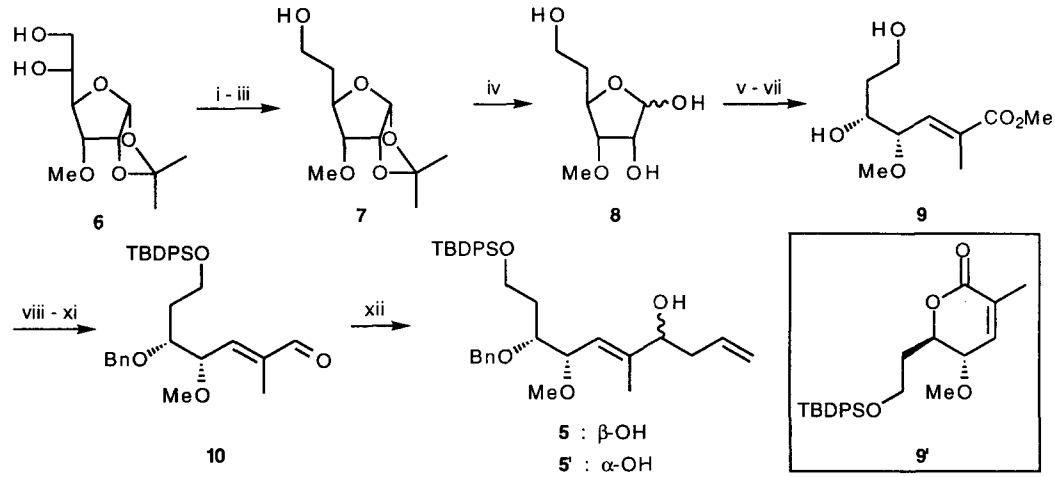
Fumagillin (**1**), an antibiotic isolated from certain strains of *Aspergillus fumagatus*,[1] has been used primarily in the control of the microspordian parasites of honey bees and fishes.[2,3] Very recently, Ingber *et al.* reported that fumagillin inhibits endothelial cell proliferation *in vitro* and tumor-induced angiogenesis *in vivo*. A semi-synthetic analog of fumagillin has just entered clinical trials for the treatment of human cancers.[4] The fascinating biological activity of fumagillin, coupled with its novel structure containing highly sensitive functionality, has stimulated the interest of several groups in synthesis. However, only one successful synthesis of fumagillin in racemic form has been published to date by Corey and Snider based on an elegant Diels-Alder strategy.[5] Described herein is the first asymmetric synthesis of fumagillol (**2**), a saponification product of fumagillin, employing a glycolate Claisen rearrangement[6] and an intramolecular ester enolate alkylation (IEEA) strategy[7] developed in our laboratories as key steps (**Scheme I**). It is worthwhile mentioning that the mono-substituted double bond in intermediate **3** is less susceptible than the more nucleophilic tri-substituted double bond to epoxidation. The terminal alkene thus can subsequently serve as a latent aldehyde functionality for a future Wittig reaction.

Scheme I



As shown in **Scheme II** our preparation of key carbohydrate-derived precursor **5** starts from known diol **6**,[8] which is readily accessible in two simple steps from commercially available 1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose. Compound **6** was converted to alcohol **7** in three steps by well-established carbohydrate chemistry. Thus, dimesylation of diol **6**, followed by treatment with NaI, produced the corresponding olefin which was hydroborated with 9-BBN to yield deoxygenated alcohol **7** in 72% overall yield for the three steps.[9,10] Acidic hydrolysis of acetonide **7**, oxidative cleavage of the resulting vicinal diol **8** with $NaIO_4$ and subsequent Wittig reaction with methyl (triphenylphosphoranylidene)propionate in acetonitrile gave dihydroxy enoate **9** after removal of the formyl group which seemed to migrate to the primary hydroxyl group (63% overall yield for the four steps). Selective protection of the primary hydroxyl group of **9** with TBDPSCl,[11] benzylation of the secondary hydroxyl group using Bundle's conditions,[12] DIBALH reduction and oxidation with activated MnO_2 produced the desired α,β-unsaturated aldehyde **10** in 74% overall yield for the four steps. Addition of allyl magnesium bromide to aldehyde **10** as expected produced an 1 : 1 mixture of alcohols **5** and **5'**, which were readily separable by silica gel column chromatography in 84% total yield.[13]

Scheme II

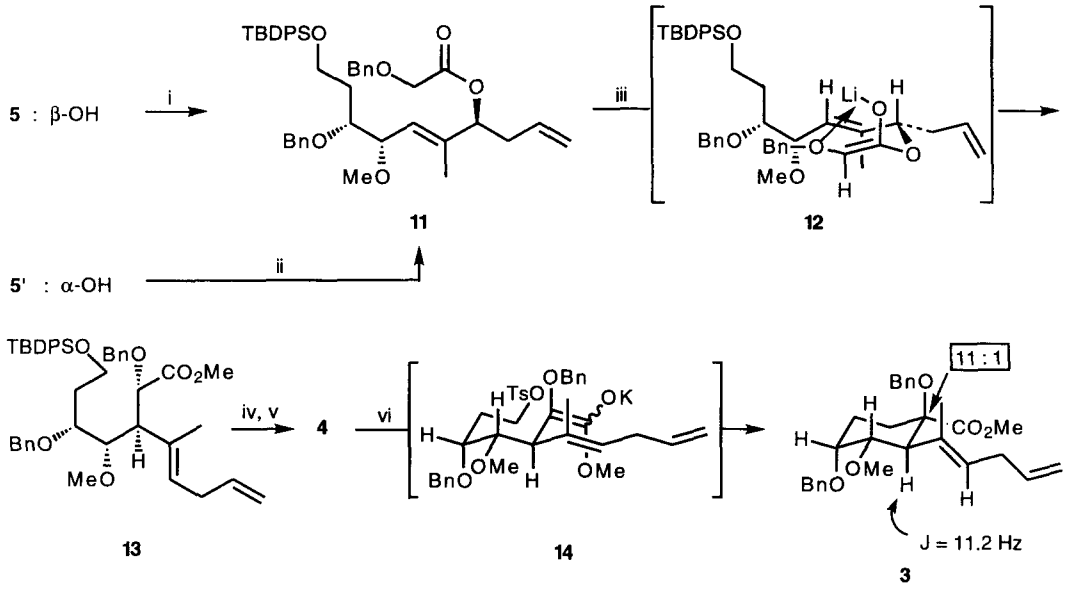


Reagents: i) MsCl, TEA, methylene chloride, -30 to -20 °C, 30 min; ii) NaI, methyl ethyl ketone, 100 °C, 9 h, (77% for 2 steps); iii) a) 9-BBN, THF, -40 °C to rt, overnight b) 30% H_2O_2, 3N NaOH, 60 to 70 °C, 2 h (93%); iv) Dowex $50x_2$-200 resin, H_2O, 100 °C, 1 h ; v) $NaIO_4$, acetone : H_2O (2 : 1), rt, 2 h; vi) $Ph_3P{=}C(CH_3)CO_2CH_3$, acetonitrile, 100 to 110 °C, 20 h; vii) K_2CO_3 (0.05 eq), methanol, rt, 4 h (63% for 4 steps); viii) TBDPSCl, DMAP (0.01 eq), TEA, methylene chloride, rt, overnight (93%); ix) $CCl_3(C{=}NH)OBn$, cat. CF_3SO_3H, cyclohexane : methylene chloride (2 : 1), rt, overnight; x) DIBALH, toluene, -78 °C, 1.5 h (89% for 2 steps); xi) MnO_2, CCl_4, rt, overnight (90%); xii) $CH_2{=}CHCH_2MgBr$, THF, -78 to 0 °C, 1 h (84%).

Both allylic alcohol **5** and isomer **5'** were converted to the desired allylic glycolate ester **11** in a single step in high yields by Steglich's DCC coupling protocol[14] and by a Mitsunobu procedure,[15] respectively (**Scheme III**). Subjection of ester **11** to the Burke-Fujisawa-Kallmerten modification[6] of the Ireland Claisen rearrangement by sequential treatment with LDA and TMSCl furnished glycolate **13** as a single diastereomer in good yield. The stereochemistry of glycolate **13** was anticipated by invoking 1,3 and 1,4 chirality transfer process through chelation-controlled chair-like transition state geometry **12**. Removal of the TBDPS group with fluoride followed by tosylation afforded internal alkylation substrate **4** uneventfully. Intramolecular ester enolate alkylation of **4** with KHMDS produced desired cyclohexanecarboxylate **3** in 61% overall yield for three steps from **13** with an 11 : 1 stereoselectivity,[10] probably through the prefered '*H-eclipsed* ' transition state

geometry **14**.[7] The large coupling constant of the allylic proton indicated by an arrow in the most stable conformation of **3**, taken together with the mechanistic rationale for the [3,3]-sigmatropic rearrangement, strongly suggests that our stereochemical assignment of allylic alcohol **5** is correct.

Scheme III

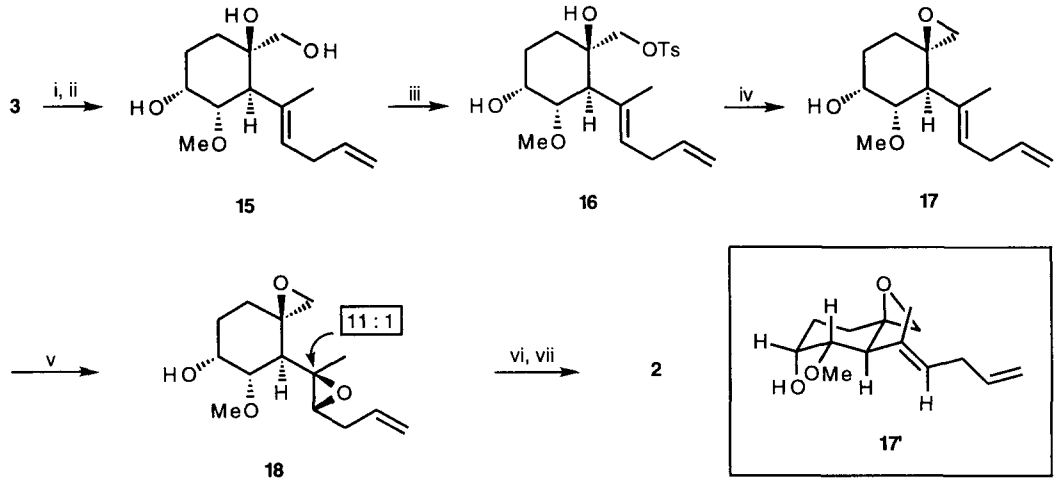


Reagents: i) $BnOCH_2CO_2H$, DMAP, DCC, methylene chloride, rt, 2 h (100%); ii) DIAD, $BnOCH_2CO_2H$, Ph_3P, THF, 0 °C to rt, 1.5 h (83%); iii) a) LHMDS, TMSCl : TEA (1 : 1.1), THF, -78 °C to rt, overnight b) Triton B, MeI, THF, rt, 2 h (89%); iv) $(n\text{-}Bu)_4NF$, THF, rt, overnight (95%); v) TsCl, pyridine, $CHCl_3$, -20 °C, overnight; vi) KHMDS, THF, -45 to -40 °C, 10 h (64% for 2 steps).

With key cyclization product **3** in hand, two epoxide functionalities were installed in succession by internal Williamson ether synthesis and *m*-CPBA epoxidation as shown in **Scheme IV**. Thus, DIBALH reduction of ester **3**, at which stage the minor stereoisomer was readily removed by silica gel column chromatography, followed by removal of the two benzyl groups with lithium in NH_3 produced a 78% yield (2 steps) of triol **15**. Mono-tosylation of triol **15**, followed by base treatment of the resulting mono-tosylate **16** produced the desired mono-epoxide **17** in 88% overall yield for the two steps. Regio- and stereo-selective epoxidation of the tri-substituted double bond of **17** with *m*-CPBA produced bis-epoxide **18** in 84% yield with 11 : 1 stereoselectivity,[10] presumably by preferential electrophilic attack on the less hindered face of the side chain appendage with a *'H-eclipsed'* conformation as illustrated in **17'**.[5] Ozonolysis of the double bond in **18**, followed by subsequent Wittig reaction with isopropylidene phosphorane, afforded the desired (-)-fumagillol (**2**) ($[\alpha]_D$ -67.4°, c 0.5, EtOH (lit. $[\alpha]_D$ -68°)) in 45% overall yield for the two steps, which was identical to an authentic sample in all respects.[16]

In summary, we have accomplished a stereoselective synthesis of (-)-fumagillol, and thus a formal synthesis of (-)-fumagillin, using an intramolecular ester enolate alkylation route in 12 steps from carbohydrate-based precursor **5**. Full accounts of our efforts to streamline the present first-generation synthesis and to evaluate medicinal chemical aspects of synthetic analogues probably unattainable from fermented fumagillin will be disclosed in due course.

Scheme IV



Reagents: i) DIBALH, toluene, -78 °C, 40 min (87%); ii) excess Li, NH_3, -78 °C, 2 min (90%); iii) TsCl, TEA, DMAP(0.04 eq), methylene chloride, rt, 12 h; iv) K_2CO_3, MeOH, rt, 4 h (88% for 2 steps); v) *m*-CPBA, $NaHCO_3$, methylene chloride, 0 °C, 4 h (92% total yield); vi) O_3, ethyl acetate, -78 °C, 1 min ; vii) excess $Ph_3P{=}C(CH_3)_2$, THF, -78 °C to rt, 2 h (45% for 2 steps)

Acknowledgements: We gratefully acknowledge generous financial support from the KOSEF and the OCRC. We thank Professors S. M. Weinreb (Pennsylvania State University), B. B. Snider (Brandeis University) and Donald Ingber (Harvard Medical School) for helpful discussions and encouragement. One of us (H. S. Kim) wishes to thank Dae Woo Foundation for a Fellowship.

References and Notes

1. Hanson, T. E., *Antibiot. Chemother.*(Washington, D. C.) **1951**, *1*, 54.
2. Girardeau, Jr., J. H. *Environ. Entomol.* **1972**, *1(4)*, 519-520.
3. Takeda Chemical Industries Jpn. Patent **1982**, 43 204; *Chem. Abstr.* **1983**, *98*, 46950m.
4. Ingber, D. E.; Fujita, T.; Kishimoto, S.; Sudo, K.; Kanamaru, T.; Brem, H.; Folkman, J. *Nature*, **1990**, *348*, 555-557; Ingber, D. E. *Semin. in Cancer Biol.* **1992**, *3*, 57-63; Folkman, J.; Ingber, D. E. *ibid.* **1992**, *3*, 89-96.
5. Corey, E. J.; Snider, B. B. *J. Am. Chem. Soc.***1972**, *94*, 2549-2550 and references cited therein.
6. Burke, S. D.; Fobare, W. F.; Pacofsky, G. J. *J. Org. Chem.* **1983**, *48*, 5221-5228; Sato, T.; Tajima, K.; Fujisawa, T. *Tetrahedron Lett.* **1983**, *24*, 729-730; Kallmerten, J.; Gould, T. J. *ibid.* **1983**, *24*, 5177-5180.
7. Kim, D.; Shin, K. J.; Kim, I. Y.; Park, S. W. *Tetrahedron Lett.* **1994**, *35*, 7957-7960 and references cited therein.; See also Stork, G. ; Zhao, K. *J. Am. Chem. Soc.* **1990**, 112, 5875-5876.
8. Haga, M.; Takano, M.; Tejima, S. *Carbohyd. Res.* **1972**, *21*, 440-446.
9. Gurjar, M.K.; Patil, V. J.;Pawar, S. M. *Carbohyd. Res.* **1987**, *165*, 313-317.
10. All new compounds exhibited satisfactory spectroscopic and analytical (high-resolution mass or combustion) data and the ratio of stereoisomers was determined by high-field ^1H NMR analysis and/or isolation of individual isomers.
11. A small amount of (*Z*)-enoate (about 5%) was present in the form of lactone **9'**.
12. Iversen, T.; Bundle, D. R. *J. Chem. Soc., Chem. Commun.* **1981**, 1240-1243.
13. The stereoselectivity could be improved by the treatment of aldehyde **10** with (*R,R*)-diisopropyl tartrate-derived allylboronate in toluene at -78 °C in the presence of 4A MS to give a 5.5 : 1 mixture of **5** and **5'** in 80% total yield: Roush, W. R.; Waltz, A. E.; Hoong, L. K. *J. Am. Chem. Soc.* **1985**, *107*, 8186-8190.
14. Steglich, W.; Neises, B. *Angew. Chem.* **1978**, *90*, 556-557.
15. Mitsunobu, O. *Synthesis* **1981**, 1-28.
16. We thank Dr. S. Terao (Takeda Chemical Industries) for a generous sample of (-)-fumagillol.

(*Received in Japan* 7 *April* 1997; *revised* 6 *May* 1997; *accepted* 9 *May* 1997)