ORGANIC LETTERS

2003
Vol. 5, No. 9
1411−1414

Systematic Synthesis of Bis-THF Ring Cores in Annonaceous Acetogenins

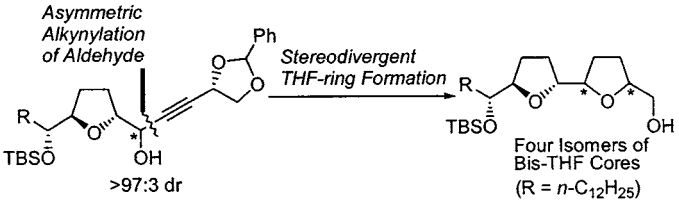
Naoyoshi Maezaki, Naoto Kojima, Hiroaki Tominaga, Minori Yanai, and Tetsuaki Tanaka*

Graduate School of Pharmaceutical Sciences, Osaka University, 1-6 Yamadaoka, Suita, Osaka 565-0871, Japan

t-tanaka@phs.osaka-u.ac.jp

Received January 23, 2003

ABSTRACT



Systematic synthesis of bis-THF ring cores, synthetic intermediates of adjacent bis-THF annonaceous acetogenins, has been achieved by asymmetric alkynylation and subsequent stereodivergent THF ring formation. The asymmetric alkynylation of α-tetrahydrofuranic aldehyde with (*S*)-3-butyne-1,2-diol derivatives gave good yields of *erythro*- and *threo*-adducts with very high diastereoselectivity. These adducts were converted into four types of bis-THF cores via two kinds of one-pot THF ring formation.

Annonaceous acetogenins are a class of natural products that have excellent antitumor, pesticidal, antimalarial, immunosuppressive, and antifeedant properties (Figure 1).[1,2] Over 350 acetogenins have been isolated from various Annonaceae plants, and they are characterized by the presence of one to three tetrahydrofuran (THF) rings with various stereochemistries in the center of a long hydrocarbon chain that has a butenolide moiety at the end. In particular, adjacent bis-THF acetogenins have attracted considerable attention, since they are biologically the most potent group among all the acetogenins.

Reiterative methodology is an effective strategy for the synthesis of acetogenins because they have repeated components. Figadère and Casiraghi developed a unique reiterative procedure based on Lewis acid-promoted *C*-glycosydation of lactol derivatives with 2-(trimethylsilyoxy)furan.[3] However, their method lacks stereoselectivity. A highly stereoselective reiterative procedure was developed by Koert utilizing nucleophilic addition of 3,4-isopropylidenedioxy-

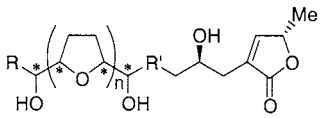


Figure 1. Representative structure of annonaceous acetogenins (*n* = 1−3, R, R′ = hydrocarbon chain having oxygenated moities and/or double bonds).

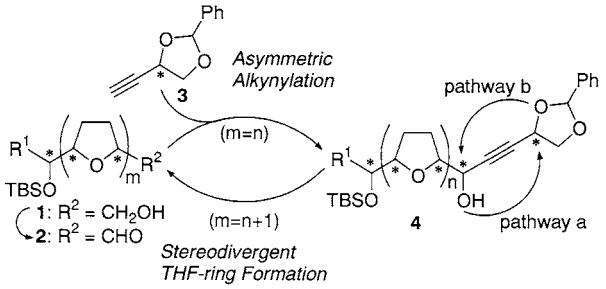
(1) For recent reviews for annonaceous acetogenins, see: (a) Alali, F. Q.; Liu, X.-X.; McLaughlin, J. L. *J. Nat. Prod.* **1999**, *62*, 504−540. (b) Zafra-Polo, M. C.; Figadère, B.; Gallardo, T.; Tormo, J. R.; Cortes, D. *Phytochemistry* **1998**, *48*, 1087−1117. (c) Cavé, A.; Figadére, B.; Laurens, A.; Cortes D. In *Progress in the Chemistry of Organic Natural Products*: *Acetogenins from Annonaceae*; Hertz, W., Eds.; Springer-Verlag: New York, 1997; Vol. 70, pp 81−288. (d) Zeng, L.; Ye, Q.; Oberlies, N. H.; Shi, G.; Gu, Z.-M.; He, K.; McLaughlin, J. L. *Nat. Prod. Rep.* **1996**, *13*, 275−306. (e) Zafra-Polo, M. C.; González, M. C.; Estornell, E.; Sahpaz, S.; Cortes, D. *Phytochemistry* **1996**, *42*, 253−271. (f) Gu, Z.-M.; Zhao, G.-X.; Oberlies, N. H.; Zeng, L.; McLaughlin, J. L. In *Recent Advances in Phytochemistry*: *ANNONACEOUS ACETOGENINS*; Arnason, J. T., Mata, R., Romeo, J. T., Eds.; Plenum Press: New York, 1995; Vol. 29, pp 249−310. (g) Fang, X.-P.; Rieser, M. J.; Gu, Z.-M.; Zhao, G.-X.; McLaughlin, J. L. *Phytochem. Anal*. **1993**, *4*, 27−67. (h) Rupprecht, J. K.; Hui, Y.-H.; McLaughlin, J. L. *J. Nat. Prod.* **1990**, *53*, 237−278.

(2) Recent reviews for a synthesis of acetogenins, see: (a) Elliott, M. C.; Williams, E. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2303−2340. (b) Elliott, M. C. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1291−1318. (c) Casiraghi, G.; Zanardi, F.; Battistini, L.; Rassu, G. *Chemtracts—Org. Chem.* **1998**, *11*, 803−827. (d) Elliott, M. C. *J. Chem. Soc., Perkin Trans. 1* **1998**, 4175−4200. (e) Figadère, B. *Acc. Chem. Res.* **1995**, *28*, 359−365. (f) Hoppe, R.; Scharf, H.-D. *Synthesis* **1995**, 1447−1464. (g) Koert, U. *Synthesis* **1995**, 115−132.

10.1021/ol034131r CCC: $25.00
Published on Web 04/03/2003

butyl anion to α-tetrahydrofuranic aldehyde. Although both *erythro*- and *threo*-adducts were obtained with high diastereoselectivities by changing the metal species, their nonchelation-controlled addition using an organozinc species gave low yield due to instability of the reagent under the reaction conditions.[4] We have recently developed a highly stereoselective and stereodivergent synthesis of mono-THF ring cores using asymmetric alkynylation of 3-butyne-1,2-diol derivative to α-oxyaldehyde.[5] The synthetic strategy is outlined in Scheme 1. One key step is Carreira's asymmetric

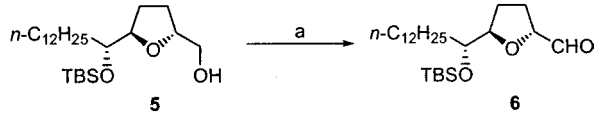
Scheme 1



alkynylation[6] to α-oxyaldehyde (**2**, $m = 0$). This strategy is potentially applicable to the reiterative construction of an oligo-THF ring system because the resulting THF ring compounds (**1**, $m = 1$) can be coupled with the C_4-unit after oxidation of the alcohol to the aldehyde. In this paper, we describe a highly stereoselective and stereodivergent synthesis of four isomers of the bis-THF ring cores, which are versatile synthetic intermediates for diverse acetogenins with potent biological activities. This is the first example of stereodivergent synthesis of a bis-THF core by reagent-controlled addition to α-tetrahydrofuranic aldehydes.[7]

The *trans*/*threo*-isomer **5** was selected as the first substrate for bis-THF ring formation since the structure was frequently found in natural adjacent bis-THF acetogenins, e.g., asimicin-type and squamocin-I-type acetogenins (Scheme 2).[1d] α-Tetrahydrofuranic aldehyde **6** was synthesized by

Scheme 2 [a]

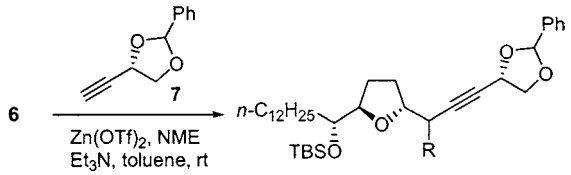


[a] Reagents and conditions: (a) Dess−Martin periodinane, pyridine, CH_2Cl_2, 0 °C to room temperature, 82%.

Dess−Martin oxidation[8] of the alcohol **5** prepared by our systematic synthesis of mono-THF ring cores.[5]

Next, we examined the asymmetric alkynylation of the aldehyde **6** with the alkyne **7**. In the reagent-controlled asymmetric alkynylation, it is very important that the reaction proceeds with high diastereoselectivity not only in the matched pair but also in the mismatched pair. As mentioned above, we have achieved the stereodivergent reagent-controlled asymmetric alkynylation of the α-oxyaldehyde, wherein high diastereoselectivity was obtained even in the mismatched pair. In this reaction, the substrates possess one stereogenic center. It is very important for establishment of the reiterative procedure that the methodology can be applied to the substrates with three stereogenic centers. The results are summarized in Table 1. Fortunately, the coupling reaction

Table 1. Asymmetric Alkynylation of Tetrahydrofuranic Aldehyde



8a: (R = β-OH)
8b: (R = α-OH)

entry	NME	yield (%)	**8a**/**8b**[a]
1	1*R*,2*S*	97	>97:3
2	1*S*,2*R*	87	3:>97

[a] Determined by ^{1}H NMR spectroscopic data.

of **6** and **7** using (1*R*,2*S*)-*N*-methylephedrine (NME), $Zn(OTf)_2$, and Et_3N in toluene proceeded smoothly to give the *threo*-adduct **8a** in good yield with very high diastereoselectivity (entry 1). We also found that *erythro*-adduct **8b** can be obtained using the antipode of NME in good yield with high diastereoselectivity.[9] To our knowledge, it is the first example that the addition to α-tetrahydrofuranic aldehydes was perfectly controlled by the chiral ligands.

Transformation of the adducts **8a** and **8b** into the bis-THF cores was conducted stereodivergently by two kinds of one-pot THF ring formation.

Scheme 3 shows the *trans*/*threo*/*trans*/*threo*-bis-THF ring formation. Hydrogenation of the triple bond accompanied

(3) (a) Zanardi, F.; Battistini, L.; Rassu, G.; Pinna, L.; Mor, M.; Culeddu, N.; Casiraghi, G. *J. Org. Chem.* **1998**, *63*, 1368−1369. (b) Figadère, B.; Peyrat, J.-F.; Cavé, A. *J. Org. Chem.* **1997**, *62*, 3428−3429.

(4) (a) Koert, U. *Tetrahedron Lett.* **1994**, *35*, 2517−2520. (b) Koert, U.; Wagner, H.; Pidun, U. *Chem. Ber.* **1994**, *127*, 1447−1457. (c) Koert, U.; Stein, M.; Harms, K. *Tetrahedron Lett.* **1993**, *34*, 2299−2302.

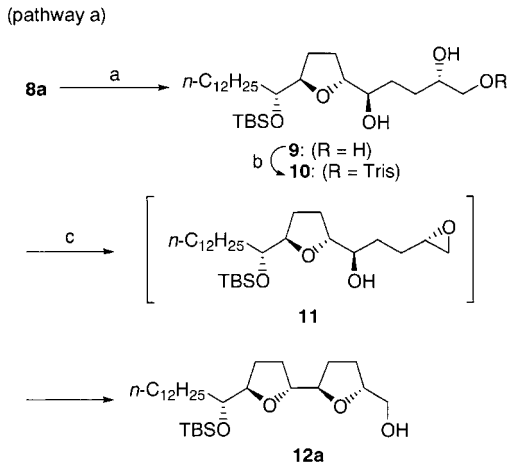
(5) Maezaki, N.; Kojima, N.; Asai, M.; Tominaga, H.; Tanaka, T. *Org. Lett.* **2002**, *4*, 2977−2980.

(6) (a) El-Sayed, E.; Anand, N. K.; Carreira, E. M. *Org. Lett.* **2001**, *3*, 3017−3020. (b) Anand, N. K.; Carreira, E. M. *J. Am. Chem. Soc.* **2001**, *123*, 9687−9688. (c) Sasaki, H.; Boyall, D.; Carreira, E. M. *Helv. Chim. Acta* **2001**, *84*, 964−971. (d) Boyall, D.; López, F.; Sasaki, H.; Frantz, D.; Carreira, E. M. *Org. Lett.* **2000**, *2*, 4233−4236. (e) Frantz, D. E.; Fässler, R.; Tomooka, C. S.; Carreira, E. M. *Acc. Chem. Res.* **2000**, *33*, 373−381. (f) Frantz, D. E.; Fässler, R.; Carreira, E. M. *J. Am. Chem. Soc.* **2000**, *122*, 1806−1807.

(7) Substrate-controlled nucleophilic addition to α-tetrahydrofuranic aldehydes was reported; see: (a) Bruns, R.; Kopf, J.; Köll, P. *Chem. Eur. J.* **2000**, *6*, 1337−1345. (b) Kuriyama, W.; Ishigami, K.; Kitahara, T. *Heterocycles* **1999**, *50*, 981−988. (c) Tian, S.-K.; Wang, Z.-M.; Jiang, J.-K.; Shi, M. *Tetrahedron*: *Asymmetry* **1999**, *10*, 2551−2562.

(8) Hoppen, S.; Bäurle, S.; Koert, U. *Chem. Eur. J.* **2000**, *6*, 2382−2396.

Scheme 3 [a]

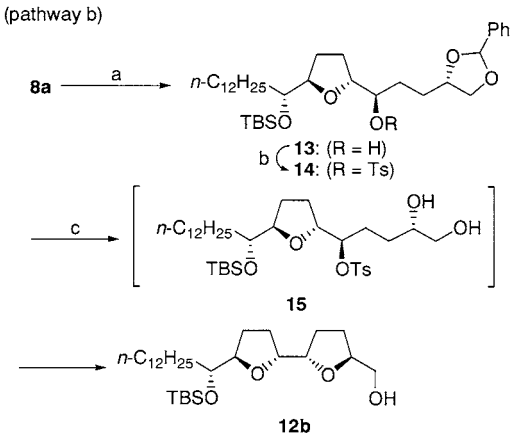


[a] Reagents and conditions: (a) H_2, 10% Pd−C, EtOAc, room temperature, 76%; (b) TrisCl, pyridine, CH_2Cl_2, 0 °C to room temperature, 71%; (c) K_2CO_3, MeOH, 0 °C to room temperature, 79%.

by deprotection of the benzylidene acetal in **8a** afforded a saturated triol **9** in 76% yield. Selective sulfonylation of the primary alcohol with 2,4,6-triisopropylbenzenesulfonyl chloride (TrisCl) gave the sulfonate **10** in 71% yield. Upon treatment of **10** with K_2CO_3 in MeOH, the THF ring formation via an epoxide **11** proceeded smoothly in a one-pot reaction to give the *trans*/*threo*/*trans*/*threo*-bis-THF ring core **12a** in 79% yield (pathway a).[10]

On the other hand, the *trans*/*erythro*/*trans*/*threo*-isomer **12b** was obtained via pathway b (Scheme 4). Tosylate **14**

Scheme 4 [a]

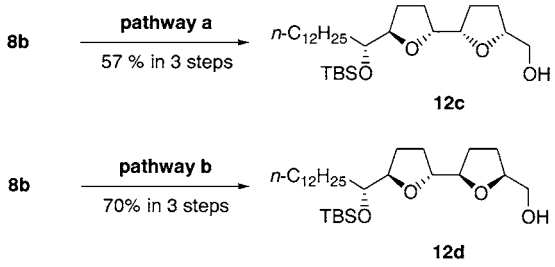


[a] Reagents and conditions: (a) H_2, 10% Pd−C, Et_3N, EtOAc, room temperature; (b) *p*-TsCl, pyridine, 0 °C to room temperature, 87% in two steps; (c) H_2, 10% Pd−C, THF, room temperature then NaH, 0 to 40 °C, 77%.

was obtained in two steps by selective reduction of the triple bond using Et_3N as catalyst poison[11] followed by tosylation of the secondary alcohol. In a previous paper concerning the mono-THF ring formation,[5] the reductive deacetalization in EtOAc and the intramolecular Williamson synthesis with NaH in THF were carried out in a stepwise manner. We found that the reaction can be performed in a one-pot reaction with THF as a solvent, giving **12b** in good yield without formation of a THP ring.

In a similar manner, a *cis*/*erythro*/*trans*/*threo*-isomer **12c** and a *cis*/*threo*/*trans*/*threo*-isomer **12d** were also synthesized from the common *erythro*-adduct **8b** in 57% and 70% overall yield, respectively (Scheme 5).

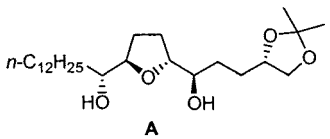
Scheme 5



In conclusion, we have developed a highly stereoselective systematic synthesis of the bis-THF ring cores in annonaceous acetogenins. Asymmetric alkynylation to the aldehyde with three stereogenic centers proceeded in good yields and with almost exclusive selectivities. It should be mentioned that high diastereoselectivity is crucial to obtain the products with high optical purity, since separation of the diastereoisomers is very difficult. Using this methodology, we have synthesized four diastereoisomers of the bis-THF cores, including the synthetic intermediate for natural adjacent bis-THF acetogenins. Moreover, since the antipodes of all chiral materials (alkyne, aldehyde, NME) are available, this methodology could be applied to synthesize various diastereoisomers of the bis-THF cores. Application of our methodology to synthesis of biologically active acetogenins is under way. These results will be reported elsewhere.

Acknowledgment. We acknowledge financial support by a Grant-in-Aid for Scientific Research (C) from the Japan

(9) The stereochemistry of **8a** was determined by comparison of the chemical shifts around the THF ring in ^{13}C NMR spectroscopic data of **A**, which was synthesized from **9** by acetalization and deprotection of the TBS group, with those of Fujimoto's synthetic model compounds. In a similar manner, the stereochemistry of **8b** was also determined. Fujimoto, Y.; Murasaki, C.; Shimada, H.; Nishioka, S.; Kakinuma, K.; Singh, S.; Singh, M.; Gupta, Y. K.; Sahai, M. *Chem. Pharm. Bull.* **1994**, *42*, 1175−1184.



(10) Recently, a one-pot THF ring formation from the 1,2,5-triol derivatives was reported by Forsyth and co-workers. (a) Dounay, A. B.; Florence, G. J.; Saito, A.; Forsyth, C. J. *Tetrahedron* **2002**, *58*, 1865−1874. (b) Dounay, A. B.; Forsyth, C. J. *Org. Lett.* **2001**, *3*, 975−978.

(11) (a) Sajiki, H.; Hirota, K. *Tetrahedron* **1998**, *54*, 13981−13996. (b) Sajiki, H. *Tetrahedron Lett.* **1995**, *36*, 3465−3468.

Society for the Promotion of Science (No. 14572006) and a grant from the Shorai Foundation for Science and Technology. N.K. is grateful for a Research Fellowship of the Japan Society for the Promotion of Science for Young Scientists.

Supporting Information Available: ^{1}H NMR spectra of compounds **8a**,**b** and **12a**−**d**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL034131R