ORGANIC LETTERS

2002
Vol. 4, No. 17
2977−2980

Highly Stereoselective and Stereodivergent Synthesis of Four Types of THF Cores in Acetogenins Using a C_4-Chiral Building Block

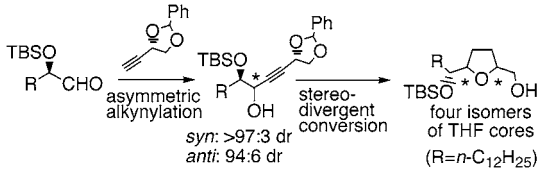
Naoyoshi Maezaki, Naoto Kojima, Mikito Asai, Hiroaki Tominaga, and Tetsuaki Tanaka*

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

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

Received June 20, 2002

ABSTRACT



Four stereoisomers of the THF cores, synthetic intermediates of acetogenins, have been synthesized with high diastereoselectivity by asymmetric alkynylation and subsequent stereodivergent THF ring formation. The asymmetric alkynylation of α-oxyaldehyde with (*S*)-3-butyne-1,2-diol derivatives (C_4-unit) gave good yields of syn and anti adducts with >97:3 dr and 94:6 dr, respectively. These adducts were converted into the four types of THF compounds via one-pot THF formation or via intramolecular Williamson synthesis.

Annonaceous acetogenins are a class of natural products possessing an oligo-THF structure with diverse stereochemistry. The polyketide natural products have attracted much attention due to their highly potent antitumor activity.[1] The potency of cytotoxicity and the spectrum against effective cancer cell lines varied depending on the structure of the THF moiety characterized by one, two, or three THF ring(s) with varying stereochemistry. Therefore, a synthetic route with high selectivity and excellent divergency is required to discover compounds with promising anticancer activity. Considerable efforts have been devoted to synthesize such compounds.[2]

Reiterative methodology is a powerful tool when the target molecules contain repeating subunits such as acetogenins. The strategy is advantageous in terms of economics (same reagents used) and ease of operation. Figadere and Casiraghies independently reported oligo-THF ring construction based on Lewis acid-promoted C-glycosylation of lactol derivatives with 2-(trimethylsiloxy)furan.[3] Their method is useful to synthesize varied collections of the oligo-THF cores but lacks stereoselectivity. Koert constructed an oligo-THF structure using nucleophilic addition of 3,4-isopropylidenedioxybutyl anion to α-oxyaldehydes. Both syn and anti adducts were synthesized with high diastereoselectivities by changing the metal species. However, their approach incurred a problem regarding the yield in the non-chelation-controlled addition using an organozinc reagent in the presence of Lewis

(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) Zeng, L.; Ye, Q.; Oberlies, N. H.; Shi, G.; Gu, Z.-M.; He, K.; McLaughlin, J. L. *Nat. Prod. Rep.* **1996**, *13*, 275−306. (d) Zafra-Polo, M. C.; González, M. C.; Estornell, E.; Sahpaz, S.; Cortes, D. *Phytochemistry* **1996**, *42*, 253−271. (e) Rupprecht, J. K.; Hui, Y.-H.; McLaughlin, J. L. *J. Nat. Prod.* **1990**, *53*, 237−278.

(2) For 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) Figadere, B. *Acc. Chem. Res.* **1995**, *28*, 359−365.

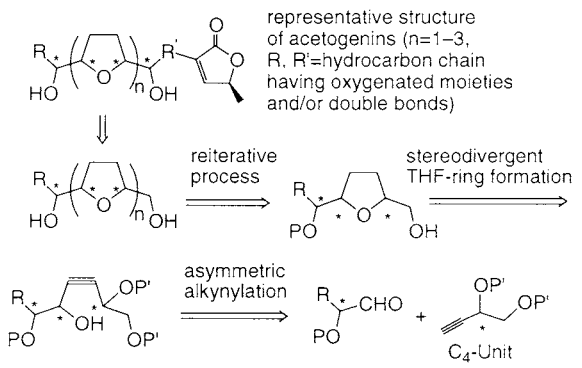
(3) (a) Zanardi, F.; Battistini, L.; Rassu, G.; Pinna, L.; Mor, M.; Culeddu, N.; Casiraghi, G. *J. Org. Chem.* **1998**, *63*, 1368−1369. (b) Figadère, B.; Peyrat, J.-F.; Cavé, A. *J. Org. Chem.* **1997**, *62*, 3428−3429.

10.1021/ol026393j CCC: $22.00
Published on Web 07/27/2002

acid due to instability of the reagent under the reaction conditions.[4]

We planned a reiterative synthesis of the oligo-THF segment based on reagent-controlled asymmetric alkynylation and stereodivergent THF ring formation as outlined in Scheme 1.

Scheme 1

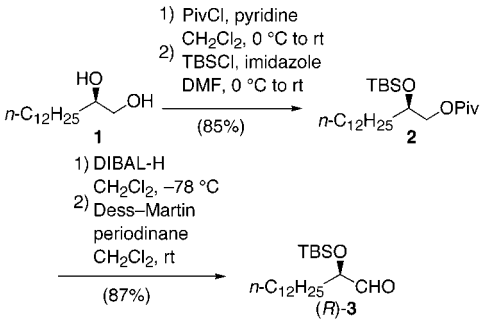


We envisaged a 3-butyne-1,2-diol derivative as a chiral C_4-unit, both enantiomers of which are readily prepared from the natural product in enantiomerically pure form. The THF ring would be constructed via asymmetric alkynylation of α-oxyaldehyde. The terminal primary alcohol in the resulting THF compound would become a junction with another C_4-unit by oxidation to the aldehyde. Therefore, this synthetic strategy can be potentially applied even to a synthesis of oligo-THF compounds. We expected high diastereoselectivity by the prominent stereodifferentiating ability of the Carreira protocol,[5] and also convenient stereocontrol by changing only the chiral ligand. One reason we employed alkynylation is that the unreacted acetylide can be reused even if the reaction required excess reagent. Such reuse is difficult in the case of an organometal reagent generated by halogen−metal exchange reaction. We also planned stereodivergent synthesis of four stereoisomers of the THF core from two common precursors by changing the protocol of THF formation.

In this paper, we describe a highly diastereoselective and stereodivergent synthesis of all four diastereomers of the THF cores flanked two hydroxy groups, which are versatile synthetic intermediates for diverse acetogenins.

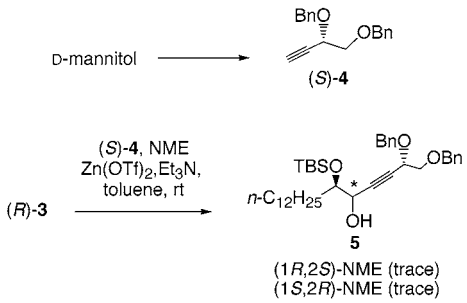
The optically pure aldehyde (*R*)-**3** was synthesized starting from (*R*)-tetradecane-1,2-diol **1** prepared by kinetic resolution of racemic 1-tetradecene oxide with Jacobsen's catalyst.[6] The diol **1** was converted into the α-oxyaldehyde (*R*)-**3** via a pivalate **2** in 74% overall yield by the usual method (Scheme 2).

Scheme 2



As alkyne components, we employed (*S*)-3-butyne-1,2-diol dibenzyl ether (*S*)-**4** prepared from D-mannitol (Scheme 3).[7] The choice of benzyl ether for diol protection has the advantage of reducing the number of steps since the deprotection and reduction of the triple bond can take place simultaneously. Unfortunately, the asymmetric alkynylation of (*R*)-**3** with the alkyne (*S*)-**4** in the presence of (1*R*,2*S*)- or (1*S*,2*R*)-*N*-methylephedrine (NME), $Zn(OTf)_2$, and Et_3N was sluggish, and only a trace amount of an adduct **5** was obtained.[8] Most of the aldehyde (*R*)-**3** was decomposed during the long reaction time (Scheme 3).

Scheme 3



We assumed that steric bulkiness of the dibenzyl moiety in the alkyne (*S*)-**4** impeded the reaction. Therefore, we examined asymmetric alkynylation of (*R*)-**3** with the alkyne having diol protection with less steric demand such as bis-acetyl and cyclohexylidene. However, the bis-acetyl compound did not afford the adduct. Although the cyclohexylidene afforded good results in a synthesis of the syn adduct (93%, >97:3 dr), the yield and selectivity for the anti adduct

(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) (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.

(6) (a) Schaus, S. E.; Brånalt, J.; Jacobsen, E. N. *J. Org. Chem.* **1998**, *63*, 4876−4877. (b) Tokunaga, M.; Larrow, J. F.; Kakiuchi, F.; Jacobsen, E. N. *Science* **1997**, *277*, 936−938.

(7) Gooding, O. W.; Beard, C. C.; Jackson, D. Y.; Wren, D. L.; Cooper, G. F. *J. Org. Chem.* **1991**, *56*, 1083−1088.

(8) From a model study using chiral lactaldehyde TBS ether and the alkyne (*S*)-**4**, we found that a combination of the (*R*)-aldehyde and (*S*)-**4** provided better yield and selectivity than that of (*S*)-aldehyde and (*S*)-**4**.

were moderate (43%, 85:15 dr). In addition, selective deacetalyzation in the presence of TBS group was difficult.

Eventually, we found that a benzylidene acetal is the best protecting group. The diastereomers of benzylidene acetal **7a** and **7b** were readily prepared by acetal exchange reaction of 3-butyne-1,2-diol **6** ($PhCH(OMe)_2$, CSA) in good yield as an approximately 1:1 diastereomeric mixture, which can be separated by column chromatography (Scheme 4).[9]

Scheme 4

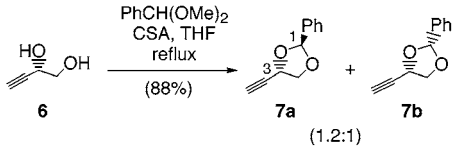
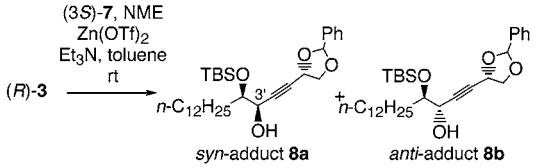


Table 1 shows the asymmetric alkynylation of the aldehyde (*R*)-**3** with the alkynes **7a** and **7b**. As expected, the reaction

Table 1. Asymmetric Alkynylation of (*R*)-**3** with (3*S*)-**7**



entry	alkyne	NME	yield (%)	**8a**:**8b**[a]
1	**7a**	1*R*,2*S*	74	>97:3
2	**7b**	1*R*,2*S*	86	95:5
3	**7a** + **7b**[b]	1*R*,2*S*	96	>97:3
4	**7a** + **7b**[b]	1*S*,2*R*	quant	6:94

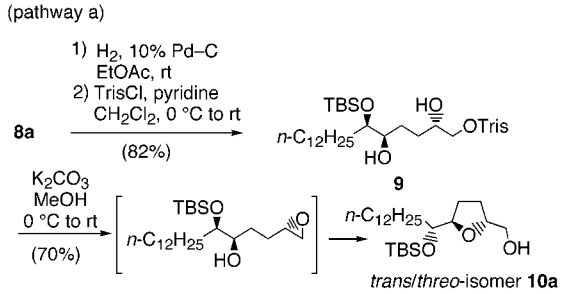
[a] Determined by ^{1}H NMR spectroscopic data. [b] Ratio of **7a**:**7b** = 1.2:1.

proceeds smoothly to give the adducts in good yield. Both diastereoisomers provided syn adducts **8a** predominantly. The C_1 stereogenic centers in the alkynes **7a** and **7b** did not show remarkable effects on either the yield or selectivity (entries 1 and 2). The results indicate that separation of **7a** and **7b** is not required in a practical operation. In fact, the syn adduct **8a** was obtained in excellent yield with very high diastereoselectivity using a mixture of **7a** and **7b** (entry 3). We also found that the anti adduct **8b** can be obtained using the antipode of NME in good yield with acceptable diastereoselectivity (entry 4).[10] Stereochemistry of the adducts was assigned by analogy with related compounds.[11,12]

With the syn and anti adducts **8a** and **8b**, respectively, in hand, we examined the stereodivergent THF ring formation. The results of trans-fused THF ring synthesis using **8a** are depicted in Schemes 5 and 6.

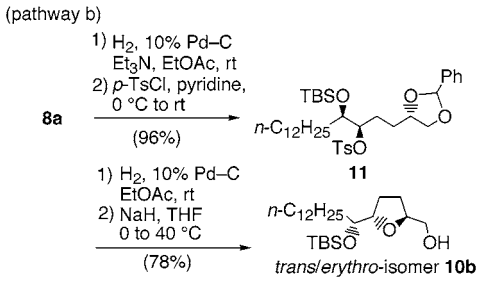
Hydrogenation of **8a** using 10% Pd−C in EtOAc afforded a saturated triol, and subsequent selective sulfonylation of the primary alcohol with 2,4,6-triisopropylbenzenesulfonyl chloride (TrisCl) furnished the sulfonate **9** in 82% yield in two steps. Upon treatment of **9** with K_2CO_3 in MeOH, the THF ring formation via an epoxide proceeded smoothly in a one-pot reaction, giving the trans/threo isomer **10a** in 70% yield (pathway a).

Scheme 5



On the other hand, the trans/erythro isomer **10b** was synthesized via pathway b (Scheme 6). Selective hydrogenation of the triple bond in the presence of Et_3N[13] followed by tosylation of the secondary alcohol transformed **8a** into a tosylate **11** in 96% yield in two steps.[14] Then, reductive deacetalyzation and subsequent intramolecular Williamson reaction using NaH in THF underwent THF ring formation rather than THP ring formation to give **10b** in 78% yield in two steps.[15]

Scheme 6



(9) The stereochemistry of the benzylidene acetal was determined by an empirical rule (Baggett, N.; Buck, K. W.; Foster, A. B.; Randall, M. H.; Webber, J. M. *J. Chem. Soc.* **1965**, 3394−3440).

(10) The diastereomeric ratio based on the benzylidene acetal for **8a** and **8b** was almost same as the ratio of **7a** and **7b** used.

(11) (a) Clive, D. L. J.; Ardelean, E.-S. *J. Org. Chem.* **2001**, *66*, 4841−4844. (b) Hirama, M.; Shigemoto, T.; Ito, S. *J. Org. Chem.* **1987**, *52*, 3342−3346.

(12) Signals of the $C_{3'}$ methine protons in ^{1}H NMR spectral data of the syn adducts **8a** appeared upfield by 0.1−0.2 ppm from those in the anti adducts **8b**. On the other hand, the signals of the OH proton in the syn adducts appeared downfield by 0.1−0.2 ppm from that in the anti adducts. The shifts were consistent for each compound in this series.

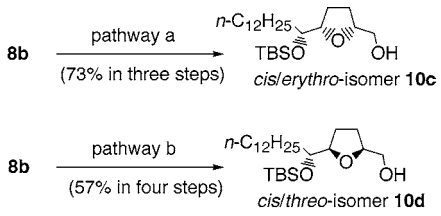
(13) (a) Sajiki, H.; Hirota, K. *Tetrahedron* **1998**, *54*, 13981−13996. (b) Sajiki, H. *Tetrahedron Lett.* **1995**, *36*, 3465−3468.

(14) An attempt to obtain **10b** via tosylation of **8a** followed by simultaneous reduction of the triple bond and the benzylidene acetal failed presumably due to hydrogenolysis of the tosyl group.

(15) Koert, U.; Stein, M.; Wagner, H. *Chem. Eur. J.* **1997**, *3*, 1170−1180 and references therein.

In a similar manner, a cis/erythro isomer **10c** and a cis/threo isomer **10d** were also synthesized from the common anti adduct **8b** in 73 and 57% overall yields, respectively (Scheme 7).

Scheme 7



Representative chemical shifts in ^{1}H and ^{13}C NMR spectral data of **10a**−**d** are summarized in Table 2. These four compounds exhibited a characteristic signal pattern, and their signals are distinguished from each other. Almost no signals due to other diastereomeric isomers were observed in each spectral data, thereby indicating the high purity of these products.

In conclusion, we have developed a highly stereoselective and stereodivergent synthesis of four types of the THF cores in acetogenins. Since the antipodes of all chiral materials (alkyne, aldehyde, NME) are available, the antipode of each isomer would be theoretically obtained. Therefore, our strategy would be applicable to synthesis of various acetogenins. Extension of this methodology to synthesis of bis- and tris-THF cores and synthetic application to biologically active acetogenins are under way. These results will be reported elsewhere.

Table 2. Representative ^{1}H and ^{13}C NMR Spectral Data of **10a**−**d**[a]

	position	*trans/threo* **10a**	*trans/erythro* **10b**	*cis/erythro* **10c**	*cis/threo* **10d**
^{1}H NMR	1	3.48, 3.65	3.46, 3.62	3.47, 3.76	3.49, 3.70
	2	4.08	4.07	4.07	4.02
	5	3.91	3.90	3.96	3.85
	6	3.57	3.76	3.59	3.78
^{13}C NMR	1	64.9	65.0	65.3	65.7
	2	79.4	79.5	79.3	79.4
	5	82.1	82.0	81.2	82.2
	6	75.0	73.4	74.7	73.1

[a] NMR spectra were recorded in $CDCl_3$ solution at 500 MHz (^{1}H) and 75 MHz (^{13}C).

Acknowledgment. We acknowledge financial support by a Grant-in-Aid for Scientific Research (C) from the Ministry of Education, Culture, Sports, Science and Technology in Japan (No. 14572006) and a grant from Shorai Foundation for Science and Technology. N.K. is grateful to Research Fellowships of the Japan Society for the Promotion of Science for Young Scientists.

Supporting Information Available: ^{1}H NMR spectra of compounds **2**−**4** and **7**−**11** and experimental procedures for **8a**, **8b**, **10a**, and **10b**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL026393J