Pergamon

Tetrahedron Letters, Vol. 37, No. 30, pp. 5393-5396, 1996

0040-4039/96 $15.00 + 0.00

PII: S0040-4039(96)01086-6

Total Synthesis of (15*S*, 16*R*, 19*S*, 20*R*, 34*S*)-Diepomuricanin[1]

Hiroyuki Konno, Hidefumi Makabe, Akira Tanaka,*† and Takayuki Oritani

Department of Applied Biological Chemistry, Faculty of Agriculture, and †Division of Environmental Bioremediation, Graduate School of Agriculture, Tohoku University, 1-1 Tsutsumidori-Amamiyamachi, Aoba-ku, Sendai 981, Japan

Abstract: An eleven-step reaction sequence starting from enantiomerically pure (-)-muricatacin (**6**) afforded the key intermediate **12**, which was then converted to (15*S*, 16*R*, 19*S*, 20*R*, 34*S*)-diepomuricanin (**1**) *via* introduction of an acetylene unit and a coupling reaction with iodo lactone synthon **15**. Copyright © 1996 Elsevier Science Ltd

Among the rapidly growing family of the Annonaceous acetogenins, that are endemic to certain plants of the *Annonaceae* and have been shown to possess a broad spectrum of biological activities involving cytotoxic, antitumor and immunosuppressive properties,[2] those bearing epoxide rings are known as biosynthetic intermediates for tetrahydrofuranic annonaceous acetogenins. Diepomuricanin (**1**), which was isolated from *Annona muricata* by A. Cavé et al.[3] is assumed to be a direct precursor for a monotetrahydrofuranic acetogenin, solamin (**2**), as depicted in Fig.1. Thus, hypothetical muricadienin (**3**) would be transformed, *via*

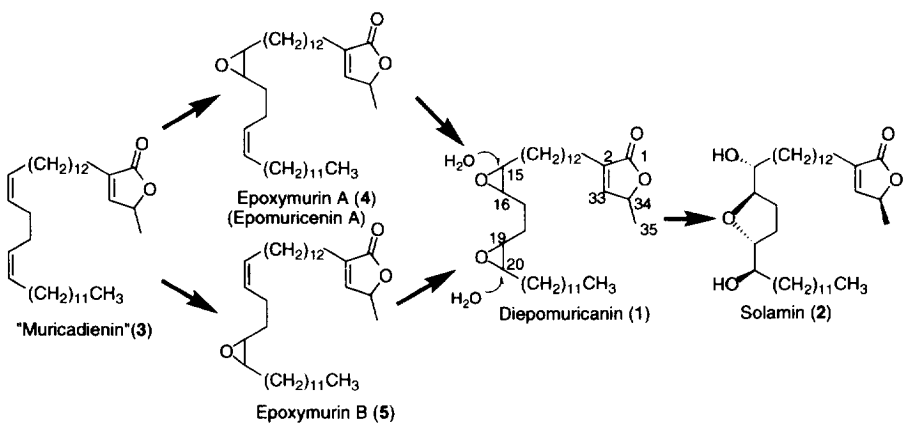


Fig. 1 Biosynthetic Pathway Proposed for Solamin (2)

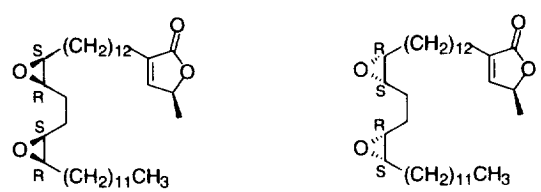
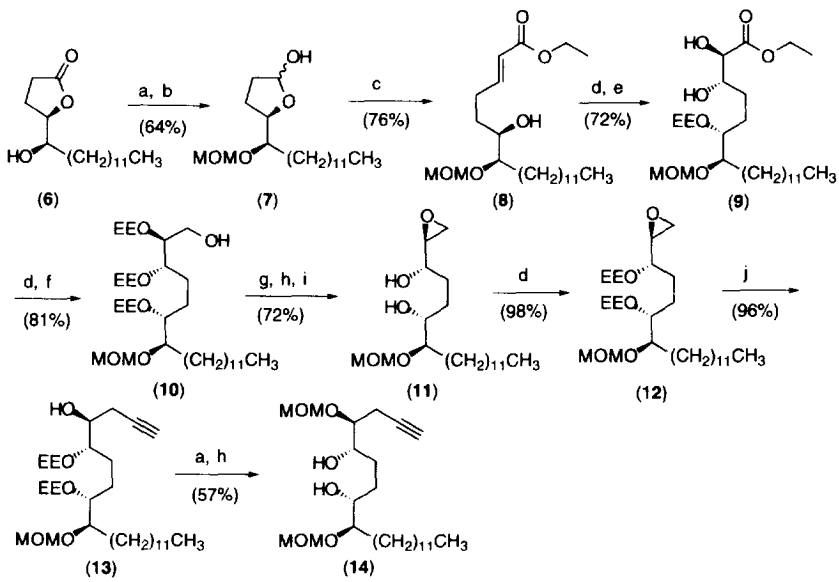


Fig. 2

epoxymurin A[4] (epomuricenin A[5]) (**4**) or epoxymurin B[4] (**5**), into diepomuricanin (**1**), which would lead to solamin (**2**) by an epoxy cascade reaction arising from the nucleophilic attack on either of the two oxirane rings of **1** by water.[4,5] Since the absolute stereochemistry of solamin (**2**) has been established by total synthesis of **2** by us[6] and others,[7] the determination of the absolute configuration of diepomuricanin (**1**) is crucial for obtaining more definite information on the biosynthetic pathway leading to solamin (**2**). Considering the *cis* stereochemistry[4] of both epoxide rings of **1**, the well-known (*S*) configuration for the secondary methyl group of the butenolide moiety and the above proposed biosynthetic pathway, there are two possible absolute stereostructures for diepomuricanin (**1**), i. e., (15*S*, 16*R*, 19*S*, 20*R*, 34*S*)-**1** and (15*R*, 16*S*, 19*R*, 20*S*, 34*S*)-**1**. In this communication, we describe a total synthesis of (15*S*, 16*R*, 19*S*, 20*R*, 34*S*)-**1** comprising a convergent approach.

The starting material was (-)-muricatacin (**6**), which had been reported earlier by us[8] and could be easily obtained in an enantiomerically pure form by recrystallization (Scheme 1). After protecting the hydroxyl group of **6** as a MOM ether, the partial reduction of the resulting lactone with DIBAL afforded acetal **7**, which was then submitted to a careful Horner-Emmons reaction at -78°C to give the chain-extended unsaturated ester **8** having the (*E*) stereochemistry. Protection of the hydroxyl group of **8** as an EE ether and subsequent Sharpless asymmetric dihydroxylation[9] using AD-mix α furnished dihydroxy ester **9**, which, after protecting the hydroxyl group of **9** with ethyl vinyl ether, was reduced with $LiAlH_4$ to yield **10**. A three-step sequence of reactions involving treatment with *p*-TsCl, hydrolysis of the EE group and oxirane ring formation with KOH provided dihydroxy epoxide **11**, which was proved to have a 92% diastereomeric excess by ^{1}H-NMR analysis. Fortunately, the undesired diastereomer could be removed from **11** by column chromatography. Protection of the hydroxyl group of **11** as an EE ether led to the key compound **12**, which underwent a coupling reaction[10] with lithium acetylide in the presence of $BF_3{\cdot}Et_2O$ to afford **13** in an excellent yield. After protection of the hydroxyl group of **13** with MOMCl and deprotection of the EE ether with PPTS, **11** gave dihydroxy acetylene

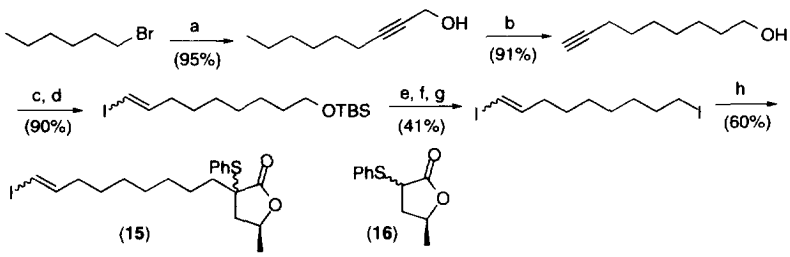


Scheme 1

a) MOMCl, i-Pr_2NEt, CH_2Cl_2 b) DIBAL, CH_2Cl_2 c) $(EtO)_2P(O)CH_2CO_2Et$, NaH, THF d) $EtOCH{=}CH_2$, PPTS, CH_2Cl_2 e) AD-mix α, $CH_3SO_2NH_2$, *t*-BuOH-H_2O f) $LiAlH_4$, Et_2O g) *p*-TsCl, pyridine h) PPTS, MeOH i) KOH j) $LiC{\equiv}CH$, $BF_3{\cdot}Et_2O$, THF

synthon **14**, ready for coupling with a lactone unit leading to the full carbon skeleton of the target molecule.

As shown in Scheme 2, the γ-lactone moiety **15** was prepared by application of the method that had been reported earlier by our group.[6]

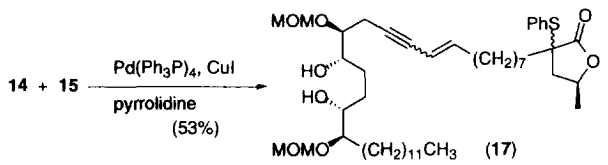


Scheme 2

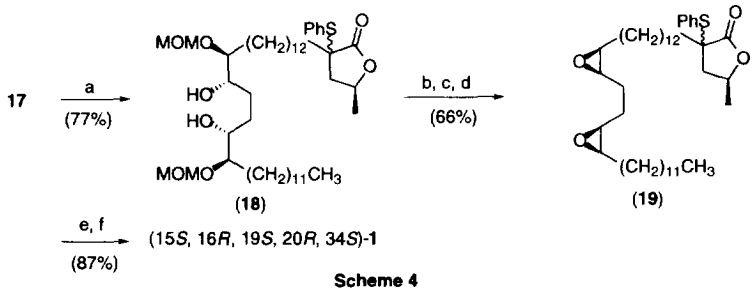
a) 2-propyn-1-ol, $LiNH_2$, liq. NH_3 b) $KNH(CH_2)_3NH_2$ c) TBDMSCl, imidazole, DMF d) *n*-Bu_3SnH, AIBN, then I_2 e) TBAF, THF f) *p*-TsCl, pyridine g) NaI, acetone h) **16**, NaHMDS, THF, HMPA

A Pd-mediated cross-coupling reaction between **14** and **15** under the reaction conditions consisting of mild treatment with $Pd(Ph_3P)_4$, CuI and pyrrolidine without any solvent[11] yielded enyne **17** (Scheme 3).

The remaining process leading to the title compound was as follows (Scheme 4). Catalytic hydrogenation of **17** with Wilkinson's catalyst gave **18**, which was then successively treated with $MsCl/Et_3N$, dil. HCl/MeOH and KOH/THF to afford **19**. Oxidation with *m*-CPBA/$NaHCO_3$ and subsequent thermal elimination by refluxing in toluene led to (15*S*, 16*R*, 19*S*, 20*R*, 34*S*)-diepomuricanin (**1**).[12] By comparing the IR, ^1H- and ^{13}C-NMR data and the optical rotation values (synthetic $[\alpha]_D$+17.0°; natural $[\alpha]_D$+13.5°), the absolute configuration of diepomuricanin is likely to be 15*S*, 16*R*, 19*S*, 20*R*, 34*S*. However, direct comparison with an authentic natural sample might be necessary in order to substantiate this identification.



Scheme 3



Scheme 4

a) H_2, $Rh(Ph_3P)_3Cl$, benzene b) MsCl, Et_3N, CH_2Cl_2 c) HCl, MeOH d) KOH(powder), THF e) *m*-CPBA, $NaHCO_3$, MeOH f) toluene, reflux

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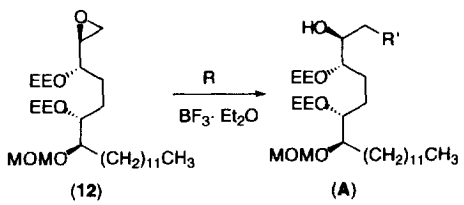
10. Treating **12** with the following various nucleophiles led to adduct **A** in only poor yields.



(12) (A)

R	(A) yield, %
LiC≡C(CH$_2$)$_{10}$OTHP	5
LiC≡C(CH$_2$)$_{10}$OTBS	5
LiC≡C(CH$_2$)$_9$CH$_3$	10
LiC≡CTMS(2 eq)	30
LiC≡CTMS(1 eq)	15

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12. Data for synthetic (15*S*, 16*R*, 19*S*, 20*R*, 34*S*)-**1**: mp 57-59°C. $[\alpha]_D^{22}$+17.0 (*c*=0.047, MeOH); +16.7 (*c*=0.30, $CHCl_3$). ^{1}H-NMR($CDCl_3$, 400 MHz) δ: 0.88 (3H, t, *J* = 6.8 Hz), 1.10-2.10 (48H, m), 1.40 (3H, d, *J* = 6.8 Hz), 2.26 (2H, ddt, *J* = 1.7, 1.7, 7.1 Hz), 2.94 (4H, m), 4.99 (1H, dtq, *J* = 1.7, 1.7, 6.6 Hz), 6.98 (1H, dt, *J* = 1.7, 1.7 Hz). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ: 14.1, 19.2, 22.7, 25.2, 23.2, 26.6, 27.3, 27.4, 27.8, 29.2, 29.3, 29.6, 29.6, 31.9, 32.5, 56.8, 57.3, 76.7, 77.0, 77.3, 134.5, 148.8, 174.0. HREIMS (M^+) Found, 546.4634. Calcd. for $C_{35}H_{62}O_4$, 546.4648.

(*Received in Japan* 11 *May* 1996; *accepted* 3 *June* 1996)