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Synthesis of (–)-(4*R*,5*R*)-muricatacin using a regio- and stereospecific ring-opening of a vinyl epoxide

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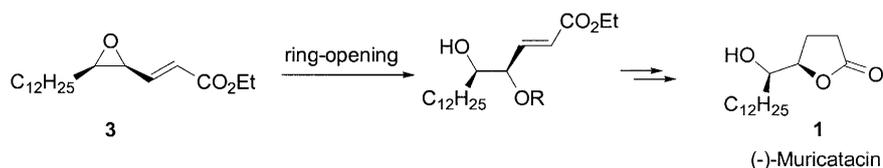
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Abstract

Total synthesis of (–)-muricatacin, a natural acetogenin, has been achieved using as a key step a regio- and stereospecific ring-opening of a substituted vinyl epoxide under Lewis acid catalysis. © 2000 Elsevier Science Ltd. All rights reserved.

Keywords: acetogenin; muricatacin; epoxide; ring-opening.

In the preceding article we presented the Lewis acid-catalyzed ring-opening of vinyl epoxides to β-hydroxy allyl-ethers.¹ To study the stereoselectivity of this reaction we have developed a new route to (–)-muricatacin **1** using the epoxide ring-opening reaction as a key step (Scheme 1).



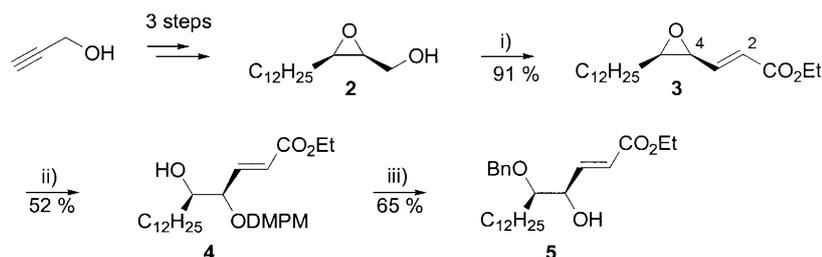
Scheme 1.

Acetogenins are natural products isolated from a worldwide family of tropical plants called Annonaceae.² Their antitumoral, immunosuppressive, pesticidal and antimicrobial bioactivities have attracted increasing interest. (–)-Muricatacin **1** is the simplest of the known native Annonaceous acetogenins related to γ-lactone and was isolated from the seeds of *Annona muricata*.³ Since its isolation in 1991, several syntheses of muricatacin⁴ and its analogs⁵ have been described in the literature.

In this paper we report an asymmetric synthesis of (–)-muricatacin **1** using our new methodology based on the opening of alkenyl epoxides. This reaction is shown to be stereospecific.

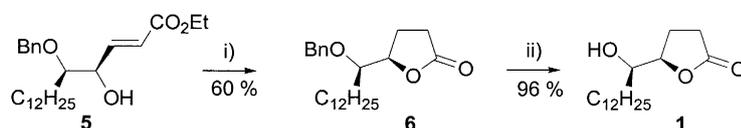
The strategy involves the preparation of the key compound **5** from functionalized vinyl epoxide **3** (Scheme 2).

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Scheme 2. (i): (a) $\text{SO}_3 \cdot \text{pyridine}$, NEt_3 , CH_2Cl_2 , DMSO ; (b) $(\text{EtO})_2\text{P}(\text{O})\text{CH}_2\text{CO}_2\text{Et}$, NaH , THF ; (ii): DMPMOH , $\text{BF}_3 \cdot \text{Et}_2\text{O}$, CH_2Cl_2 ; (iii): (a) NaH , BnBr , DMF ; (b) DDQ , $\text{CH}_2\text{Cl}_2/\text{H}_2\text{O}$

(2*S*,3*R*)-2,3-Epoxy-pentadecanol **2**⁶ was prepared in three steps from propargylic alcohol as previously described in the literature.^{4d} Oxidation of epoxyalcohol **2** using $\text{SO}_3 \cdot \text{pyridine}$ in $\text{CH}_2\text{Cl}_2:\text{DMSO}$ (5:1) afforded the corresponding epoxyaldehyde, which was immediately subjected to olefination with triethylphosphonoacetate giving α,β -unsaturated ester **3** in 91% yield. Treatment of **3** with one molar equivalent of 3,4-dimethoxybenzylalcohol (DMPMOH) following the previously reported procedure,¹ allowed access to alcohol **4** in 52% yield.⁷ This yield is slightly lower than those obtained using nonsubstituted vinyl epoxides,¹ but is still good considering the five consecutive electrophilic centers (C1 to C5) present in compound **3**. In order to study the stereoselectivity of the ring-opening reaction, alcohol **4** was treated with NaH and benzylbromide followed by selective deprotection with DDQ to lead to allylic alcohol **5** in 65% yield. Compound **5** was then esterified by both *R* and *S* Mosher's reagents.⁸ The ^{19}F NMR of the MTPA-esters showed that the enantiomeric excess was $>98\%$. Measurements of the $\Delta\delta$ taken from ^1H NMR spectroscopy using $^1\text{H}-^1\text{H}$ COSY allowed the assignment of the absolute configuration⁹ of stereocenter C4. The values of $\Delta\delta$ obtained are in accordance with an *R* configuration.¹⁰ With respect to these experimental results, the reaction appears to be stereospecific and to proceed with an inversion of configuration in the reaction center. The reaction mechanism therefore follows an $\text{S}_{\text{N}}2$ pathway as expected. Using enantio-assigned alcohol **5**, the synthesis of (–)-muricatacin **1** was achieved as reported in Scheme 3.



Scheme 3. (i): (a) $\text{Ni}(\text{OAc})_2$, NaBH_4 , EtOH ; (b) *p*- TSOH , C_6H_6 ; (ii): H_2 , Pd/C , EtOH

Compound **5** was hydrogenated in the presence of a P-2 nickel catalyst using a known procedure.^{4j} Lactonization to **6** was completed by treatment of the crude product with *p*-toluenesulfonic acid in benzene. Finally, benzyl ether **6** was deprotected to give the desired (4*R*,5*R*)-muricatacin **1**. The spectroscopic data (^1H and ^{13}C NMR, IR, MS) and the optical rotation of **1** were in close agreement with reported values (obs. $[\alpha]_{\text{D}}^{21} = -22$, $c=0.5$, CHCl_3 ; lit. $[\alpha]_{\text{D}}^{25} = -23.3$, $c=0.5$, CHCl_3).^{4j} More conveniently, hydrogenation of **4** followed by treatment with trifluoroacetic acid^{5a} afforded muricatacin **1**.

In summary, a novel and enantiospecific synthesis of (4*R*,5*R*)-muricatacin has been accomplished using a regio- and stereospecific opening of substituted epoxide **3** with one molar equivalent of DMPMOH. Our strategy allows the synthesis of all possible stereoisomers of muricatacin **1**. Indeed all the stereoisomers of **2** can be easily prepared by Sharpless epoxidation on *Z* or *E* allylic alcohol using (+)-DET or (–)-DET.

Condensation of alcohol on vinyl epoxide using equal amounts of both partners has not previously been reported in the literature. Our investigations permitted this regio- and stereospecific ring-opening reaction using catalytic amounts of $\text{BF}_3 \cdot \text{Et}_2\text{O}$. This methodology allows the preparation of useful asymmetric intermediates as illustrated by the synthesis of (–)-muricatacin.

