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

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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) $SO_3 \cdot pyridine$, NEt_3 , CH_2Cl_2 , DMSO; (b) $(EtO)_2P(O)CH_2CO_2Et$, NaH, THF; (ii): DMPMOH, $BF_3 \cdot Et_2O$, CH_2Cl_2 ; (iii): (a) NaH, BnBr, DMF; (b) DDQ, CH_2Cl_2/H_2O

(2S,3R)-2,3-Epoxypentadecanol 2⁶ was prepared in three steps from propargylic alcohol as previously described in the literature.^{4d} Oxidation of epoxyalcohol **2** using SO₃·pyridine in CH₂Cl₂: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 ¹⁹F NMR of the MTPA-esters showed that the enantiomeric excess was >98%. Measurements of the $\Delta\delta$ taken from ¹H NMR spectroscopy using ¹H–¹H 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 $S_N 2$ pathway as expected. Using enantio-assigned alcohol $\mathbf{5}$, the synthesis of (-)-muricatacin $\mathbf{1}$ was achieved as reported in Scheme 3.



Scheme 3. (i): (a) Ni(OAc)₂, NaBH₄, EtOH; (b) p-TSOH, C₆H₆; (ii): H₂, 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 (4R,5R)-muricatacin **1**. The spectroscopic data (¹H and ¹³C NMR, IR, MS) and the optical rotation of **1** were in close agreement with reported values (obs. $[\alpha]_D^{21} = -22$, c=0.5, CHCl₃; lit. $[\alpha]_D^{25} = -23.3$, c=0.5, CHCl₃).^{4j} More conveniently, hydrogenation of **4** followed by treatment with trifluoroacetic acid ^{5a} afforded muricatacin **1**.

In summary, a novel and enantiospecific synthesis of (4R,5R)-muricatacin has been accomplished using a regio- and stereospecific opening of substituted epoxide **3** with one molar equivalent of DMP-MOH. 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 $BF_3 \cdot Et_2O$. This methodology allows the preparation of useful asymmetric intermediates as illustrated by the synthesis of (–)-muricatacin.

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- 6. (2*S*,3*R*)-2,3-Epoxypentadecan-1-ol **2** was recrystallized from hexane:CH₂Cl₂ (4:1). ¹⁹F NMR of Mosher's esters showed ee's >98%.
- Spectroscopic data of 4: [α]_D²⁰=-19 (*c*=1.58, CHCl₃); ¹H NMR (300 MHz, ref. CHCl₃, δ ppm): 6.87–6.77 (m, 4H), 6.06 (dd, *J*=0.9, 15.8 Hz, 1H), 4.57 (d, *J*=11.2 Hz, 1H), 4.28 (d, *J*=11.2 Hz, 1H), 4.21 (q, *J*=5.4 Hz, 2H), 3.87 (s, 3H), 3.86 (s, 3H), 3.80–3.74 (m, 1H), 3.56–3.51 (m, 1H), 2.51 (d, *J*=3.7 Hz, 1H), 1.30 (t, *J*=7.1 Hz, 3H), 1.25–1.21 (m, 22H), 0.86 (t, *J*=6.7 Hz, 3H); 13C NMR (75 MHz, ref. CDCl₃, δ ppm): 165.8, 149.1, 148.9, 144.6, 130.0, 124.5, 120.6, 111.3, 111.0, 81.7, 73.3, 71.4, 60.6, 55.9, 32.7, 31.9, 29.6, 29.3, 25.5, 22.6, 22.3, 14.2, 14.0; IR (NaCl, cm⁻¹): 3522, 2925, 2854, 1720, 1516, 1265, 1031; HRMS (LSIMS⁺): (M⁺) calcd for C₂₈H₄₆O₆: 478.3294, found 478.3280.
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- 10. $\Delta\delta$ (ppm, 500 MHz) values for the *R* and *S* MTPA esters of **5** shown in Fig. 1



Fig. 1.