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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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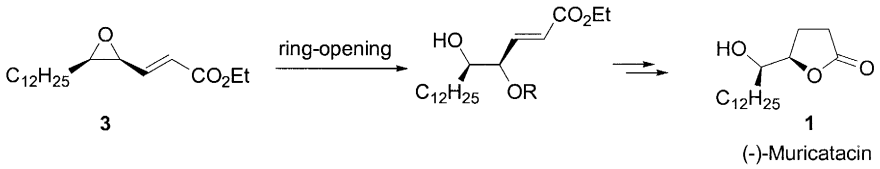
Abstract

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.

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 muricatacin[4] and its analogs[5] 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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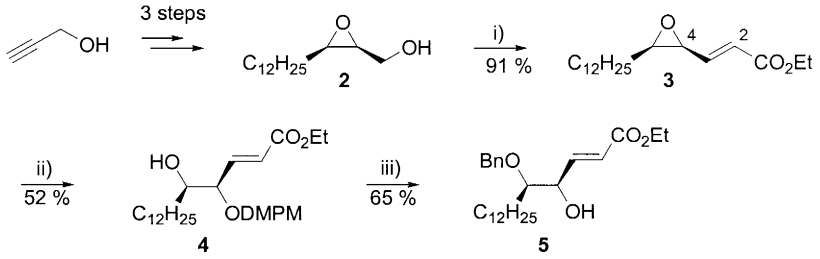
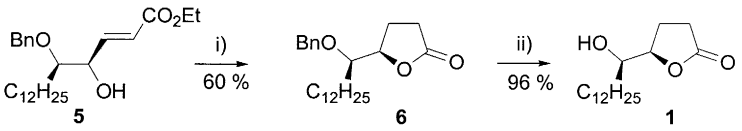


Scheme 2. (i): (a) SO_3·pyridine, NEt_3, CH_2Cl_2, DMSO; (b) $(EtO)_2P(O)CH_2CO_2Et$, NaH, THF; (ii): DMPMOH, $BF_3·Et_2O$, CH_2Cl_2; (iii): (a) NaH, BnBr, DMF; (b) DDQ, CH_2Cl_2/H_2O

(2*S*,3*R*)-2,3-Epoxypentadecanol **2**[6] was prepared in three steps from propargylic alcohol as previously described in the literature.[4d] Oxidation of epoxyalcohol **2** using SO_3·pyridine in CH_2Cl_2: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 ^1H–^1H COSY allowed the assignment of the absolute configuration[9] 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_N2 pathway as expected. Using enantio-assigned alcohol **5**, the synthesis of (−)-muricatacin **1** was achieved as reported in Scheme 3.



Scheme 3. (i): (a) $Ni(OAc)_2$, $NaBH_4$, 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. $[\alpha]_D^{21}=-22$, c=0.5, $CHCl_3$; lit. $[\alpha]_D^{25}=-23.3$, 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 $BF_3·Et_2O$. This methodology allows the preparation of useful asymmetric intermediates as illustrated by the synthesis of (−)-muricatacin.

Acknowledgements

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6. (2*S*,3*R*)-2,3-Epoxypentadecan-1-ol **2** was recrystallized from hexane:CH_2Cl_2 (4:1). ^{19}F NMR of Mosher's esters showed ee's >98%.
7. Spectroscopic data of **4**: $[\alpha]_D^{20}=-19$ (c=1.58, $CHCl_3$); ^1H NMR (300 MHz, ref. $CHCl_3$, 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. $CDCl_3$, 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 $C_{28}H_{46}O_6$: 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

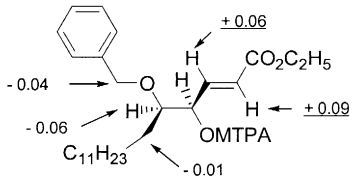

Fig. 1.