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Transition Metal Promoted Acetylene Isomerisation Reactions In Organic Synthesis: A Synthesis of (+)-(4S,5S) - Muricatacin

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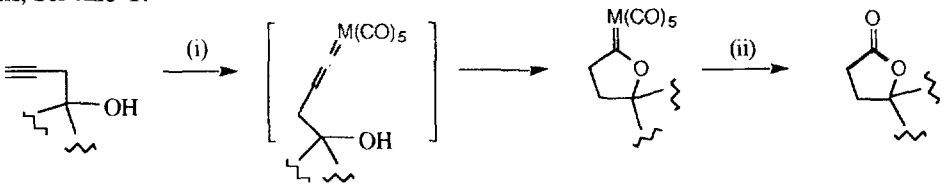
Abstract: *An acetylene - vinylidene rearrangement has been employed as a key step in the enantiospecific synthesis of (+)-(4S,5S) - muricatacin.*

Recently much effort has been devoted to the synthesis of the Annonaceous acetogenins, a family of tetrahydrofuran derivatives with antitumour and pesticidal activity.[1] In this *Letter*, we wish to communicate an enantiospecific synthesis of (+)-(4S,5S)-muricatacin (**8**)[2] which utilises our recently described γ - butyrolactone synthesis, **Scheme 1**.[3]

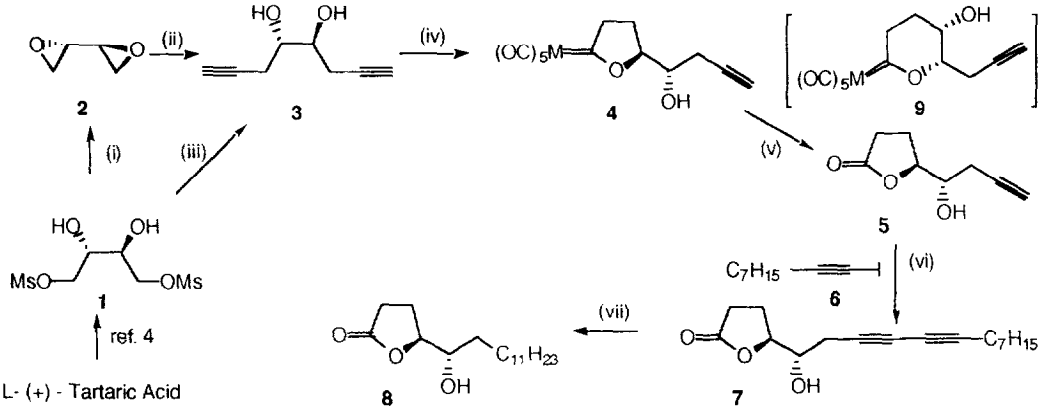


Reagents and conditions: (i) $M(CO)_5$.THF, THF, 25 °C(ii) CAN, CH_3COCH_3.

Scheme 1

We envisaged that the acetylenic lactone (**5**) could serve as a key intermediate for the synthesis of a number of acetogenins and that (**5**) could itself be prepared from the corresponding diol (**3**) by way of the carbene complex (**4**), **Scheme 2**. Although treatment of the known, enantiopure bis-epoxide (**2**)[4] with lithium acetylide - ethylenediamine complex under carefully controlled conditions (2.2 eq.; THF - DMSO (1:10); 0 °C)[5] afforded the diol (**3**)[6] ($[\alpha]_D^{20}$ + 20.1° (c = 7; $CHCl_3$)) as a white crystalline solid, mp 97-99 °C in acceptable yield (57% after recrystallisation), the preparation and isolation of (**2**) was itself problematical. A more practical route to (**3**) involved *in situ* generation and trapping of (**2**) by reaction of the crystalline bis-mesylate[4] (**1**) with lithium acetylide-ethlylenediamine complex (4.4 eq.; DMSO, 0 °C) which afforded the diol (**3**) in 87% overall yield with > 95% ee.[7] Treatment of the bis - acetylene (**3**) with a pre-formed solution of either $Cr(CO)_5$.THF or $W(CO)_5$.THF in THF (2 eq., 20 °C, 21.5 and 6.5 hrs. respectively) generated the stable carbene complexes (**4a**, M = Cr; **4b**, M=W) which were usually oxidised (CAN; 1 eq.; in dry acetone; 20 °C; 3 hrs.) without further purification to the corresponding γ-butyrolactone (**5**) ($[\alpha]_D^{23}$+35° (c = 3.2; $CHCl_3$)) in good overall yield (68%

and 74% respectively). Of note is the observation that the γ - butyrolactone (**5**) was formed in preference to the δ-valerolactone (**9**), and that protection of the free hydroxyl group was not required. Coupling of the acetylene (**5**) with the acetylenic iodide (**6**)[8] using Wityak's procedure ((**6**), 1.1 eq.; $[Pd(Ph_3P)_2Cl_2]$, 3 mol%; CuI, 3 mol%; di-isopropylamine, 1.8 eq.; THF; 45 °C; 1.25 hrs.)[9] afforded the conjugated acetylene (**7**) ($[\alpha]_D^{25}$ + 21.9° (c = 0.9; $CHCl_3$)) in 82% yield which was then subjected to catalytic hydrogenation (H_2, 4 atm.; EtOAc; 10% Pd/C; 20 °C; 16 hrs.) to afford (+) - muricatacin (**8**), mp 65-66 °C (lit[2]. mp 65 °C) whose spectral data and optical rotation ($[\alpha]_D^{23}$ + 23.6 ° (c 1.6; $CHCl_3$; lit[2b] $[\alpha]_D^{20}$ +23° (c. 1.26; $CHCl_3$)) were identical to the published data.



Reagents and conditions: (i) KOH, 2.2 eq.; Et_2O; 20 °C; 79%; (ii) lithium acetylide-EDA complex, 2.2 eq.; THF-DMSO (1:10), 0 °C; 57% ; (iii) lithium acetylide-EDA complex, 4 eq.; DMSO; 0 °C; 87%; (iv) a. $Cr(CO)_5$.THF, 2 eq.; THF; 20 °C; b. $W(CO)_5$.THF, 2 eq.; THF; ; (v) a. CAN, 1 eq.; acetone, 20 °C; 3 hrs.; 68% overall from (**3**); b. CAN, 1 eq.; acetone; 20 °C; 40 min.; 74% overall from (**3**) (vi) (**6**), $(Ph_3P)_2PdCl_2$, 3mol%; CuI, 3 mol%; DIPA, 1.8 eq.; THF; 45 °C; 1.25 hrs.; 82%; (vii) H_2, 10% Pd/C; EtOAc; 20 °C; 16 hrs.; 94%.

Scheme 2

In summary we have demonstrated that acetylenic γ- butyrolactones can be readily prepared in homochiral form from β-hydroxy acetylenes without loss of stereochemical integrity using an acetylene - vinylidene rearrangement. Acetylenic lactones serve as useful synthetic intermediates as demonstrated by their conversion into (+) - muricatacin. Application of this basic scheme to the synthesis of more complex acetogenins is now under investigation.

Acknowledgements

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References and notes

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2. **a**. For previous approaches see Figadere, B.; Harmange, J. C.; Laurens, A.; Cave, A. *Tetrahedron Letters*, **1991**, *32*, 7539; **b**. Somfai, P. *J. Chem. Soc., Perkin Trans.* 1, **1995**, 817 and refs. therein.
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5. c.f. Takano, S.; Hatakeyama, S.; Saijo, K. *Tetrahedron Letters*, **1985**, *26*, 1333. In our hands using the reaction conditions described above, the addition of $BF_3.OEt_2$ complex as activator was unnecessary.
6. All new compounds were fully characterised by ^1H and ^{13}C nmr, ir, high resolution mass spectrometry and/or combustion microanalysis.
7. As determined *via* the Mosher ester of the mono benzylether.
8. Prepared according to Nicolau, K. C.; Zeng, A. L.; McComb, S. *J. Am. Chem. Soc.*, 1992, **114**, 9279.
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