Pergamon

Tetrahedron Letters 40 (1999) 697–700

TETRAHEDRON LETTERS

An Improved Method for the Formation of Formaldehyde Acetal Derivatives from Annonaceous Acetogenins [1]

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Received 13 October 1998; accepted 19 November 1998

Abstract : Preparations of 1,2-, 1,3-, 1,5-formaldehyde acetals from the corresponding polyhydroxylated annonaceous acetogenins were performed in good yield. Addition of Et_3N to a mixture of DMSO and TMSCl is crucial to avoid *in situ* hydrolysis of the intramolecular acetals.

Keywords : acetogenins; diols; acetals.

Several species of the Annonaceae family yield a group of bioactive secondary metabolites known as annonaceous acetogenins. These polyketide compounds have shown promising anticancer activity as well as, antiparasitic, and pesticidal properties [2]. Annonaceous acetogenins have several stereogenic centers, and indeed, some acetogenins are differentiated from each other only by their configurations. Therefore stereochemical relationships between these stereogenic centers remain the most important but most difficult task in the structural elucidations, particularly for isolated hydroxyl groups, of these natural products.

Monoalcohols can be converted into intermolecular formaldehyde acetals using DMSO/PPA [3], DMSO/Br_2 [4], and DMSO/TMSCl [5]. 1,2 Diols can form intramolecular formaldehyde acetals when treated with DMSO/CH_2Br_2/KOH [6], DMSO/NBS [7] and DMSO/$POCl_3$ or $SOCl_2$ [8]. McLaughlin *et al* [9] reported that using Pinnick's procedure [5], 1,2-, 1,4- and 1,5-diols of acetogenins were converted into cyclic intramolecular formaldehyde acetals, however in low yieds (11-30%). The ^1H NMR analysis of the corresponding cyclic derivatives [2] allowed them to deduce the relative configurations of the stereogenic centers of the acetogenins [9,10].

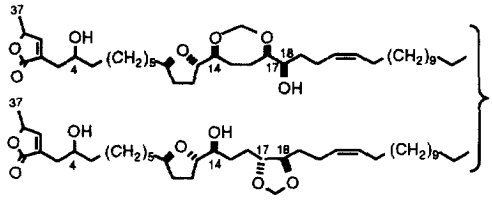
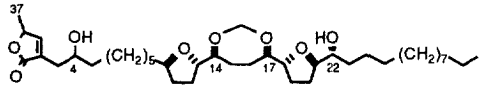
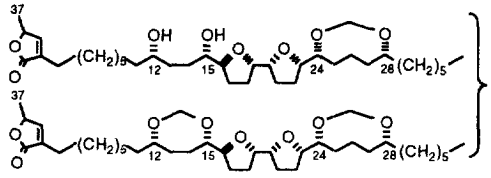
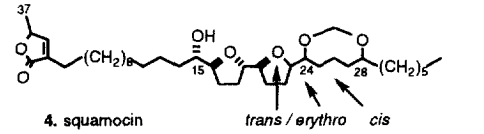
However, because the annonaceous acetogenins are isolated in very small quantities, the chemical transformations must be very efficient for further analyses by ^1H NMR. Therefore most of the absolute and relative configuration of isolated hydroxyls of acetogenins remain undefined.

We wish to report in this communication an improved methodology for the formation of intramolecular acetals in good yields, which allows the determination of relative stereochemical relationships between 1,n-diols of acetogenins (Table 1).

[1] Part 77 in the series "Acetogenins from the Annonaceae". For part 76, see ref.1.

0040-4039/99/$ - see front matter
PII: S0040-4039(98)02484-8

Table 1.

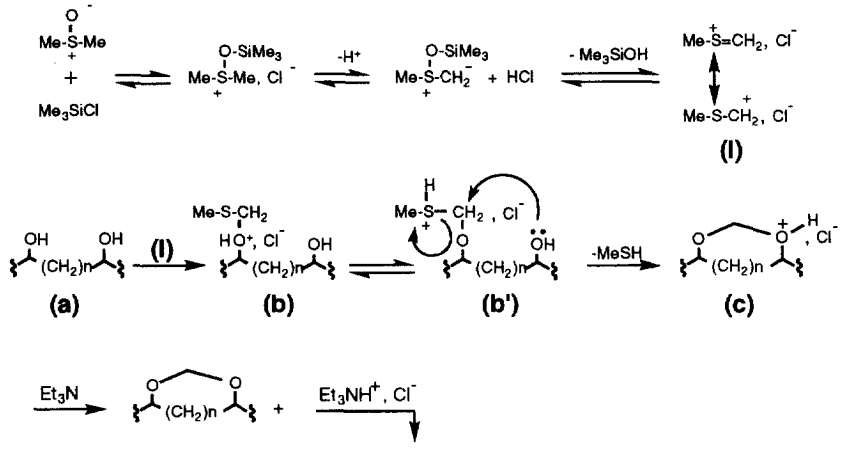
Entry	Products	Diols	Yield (%)
1	 1. gigantetronenin	1,4	20%
		1,2	39%
		(1,2) + (1,4) =	59%
2	 2. gigantecin	1,4	59%
3	 3. salzmanin	1,5	25%
		1,4 and 1,5	49%
		(1,5) + (1,4 and 1,5) =	74%
4	 4. squamocin *trans / erythro cis*	4. 1,5	52% [a]
5	5. carolin-A *cis / erythro cis*	5. 1,5	49%

[a] ref. [8] = 28.3 %

By mixing separately acetogenins (gigantetronenin [11], gigantecin [12], salzmanin [13], squamocin [14], carolin-A [15]) in DMSO with TMSCl and Et_3N at room temperature for 7 h, the corresponding acetals were obtained in good yields. The typical procedure is as follow : to Me_3SiCl (1 mL) was added Me_2SO (1 mL), and the mixture was stirred at room temperature under nitrogen for about 1 h until a white precipitate appeared. The excess of unreacted reagents was decanted, and the white precipitate was quickly washed with 1 mL of CH_2Cl_2. A solution of the acetogenin (6-10 mg) in CH_2Cl_2 (2 mL) and an excess of Et_3N (0.5 mL, about 280 equiv.) were added to this precipitate and stirred at room temperature for 7 h. When the reaction was complete as estimated by TLC, the mixture was washed using 1% $NaHCO_3$ (5 mL) and H_2O (2 x 5 mL).The separated aquous layer is then washed 3 times with 5 mL of CH_2Cl_2. The combined CH_2Cl_2 layers were dried over $MgSO_4$ and evaporated *in vacuo* after filtration The crude product was then purified by HPLC using a μBondapak C18 prepacked columm (10 μm, 25 x 100 mm) eluted with MeOH:H_2O (95:5 or 93:7), flow rate 10 mL/min, UV detection at 214 nm. Yields were calculated for the purified acetals and are ranging from 49% to 74%. The remaining mass balance is formed by the starting material.

These results (Table 1) show that all possible acetals were formed in good yields (entry 1-5), and as expected 1,2-diols are more reactive than 1,4-diols (entry 1) [9]. With salzmanin we noted that 1,5- are more reactive than 1,4-diols (entry 3), which is opposite to that observed with squamostatin [9] .

In the absence of Et_3N, authors have proposed a mechanism in which two molecules of HCl were formed [5,10]. They thus explained the low yields obtained by partial hydrolysis of the acetals by HCl. Therefore, by introduction of Et_3N in the reaction mixture, the decomposition of the acetal rings due to hydrolysis reaction was limited.



Scheme 1. Proposed mechanism for the formation of intramolecular acetals upon addition of Et_3N.

Indeed, during the preparation of the speculative reactive species **(I)** (scheme 1), one molecule of HCl was formed, which was partially eliminated during the purification process of the white precipitate of **(I)**. In the next step, an O-alkylation reaction between **(a)** and **(I)** takes place, leading to the formation of two tautomeric forms, **(b)** and **(b')**. Then an intramolecular O-alkylation reaction gives **(c)** which after elimination of MeSH and one equivalent of HCl, which is trapped by Et_3N, leads to the desired acetal. Therefore, the formation of the Et_3N hydrochloride prevents hydrolysis of the so formed acetals. However, further experiments would be necessary in order to prove this mechanism. It is worth noting that we did not observe any oxidized product which could have been formed by oxidation through a Swern type mechanism [15].

In conclusion, treatment of 1,2- to 1,5-diols by a mixture of DMSO, TMSCl and Et_3N, allowed us to obtain the desired acetals in good yields, even on very small scales. Then, ^1H NMR of the so formed cyclized products [16] allowed us to determine the relative configurations of the 1,2-, 1,4-, and 1,5-diols. This method will probably find further applications in synthesis of natural products.

Acknowledgments :

The authors express their gratitude to Jacqueline Mahuteau and Jean-Christophe Jullian for NMR measurements, Dr. Olivier Laprévote and Laurent Serani (ICSN, Gif-sur-Yvette, France) for MS/MS measurements. E.F.Q. and E.L.M.S. acknowledge the CNPq (Brazil) for financial support.

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[16] All new compounds were fully characterized by spectroscopic means (MS-MS, ^{1}H and ^{13}C NMR, IR)