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First Preparation Of 5-Allyl-1,3-Oxazolidine-2-Thione (Napoleiferin), A Natural Homolog Of 5-Vinyl-1,3-Oxazolidine-2-Thione(Goitrin)

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FIRST PREPARATION OF 5-ALLYL-1,3-OXAZOLIDINE-2-THIONE (NAPOLEIFERIN), A NATURAL HOMOLOG OF 5-VINYL-1,3-OXAZOLIDINE-2-THIONE (GOITRIN)

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Abstract: The preparation of 5-allyl-1,3-oxazolidine-2-thione (napoleiferin) **5** via a practical synthesis of but-3-enal **2** and the key intermediate 1-aminopent-4-en-2-ol **4** is described for the first time.

Glucosinolates **1** are an important class of compounds widely distributed in all crucifer plants [1-3]. Much work has been devoted to rape: the meal remaining after oil extraction can be fed to livestock, but in limited amounts since it contains antinutritional compounds, particularly glucosinolates. During seed processing, they are destroyed by an endogenous enzyme, myrosinase [E.C. 3.2.3.1] to give different products depending on parameters such as pH conditions, temperature, metal traces ... (Scheme 1).

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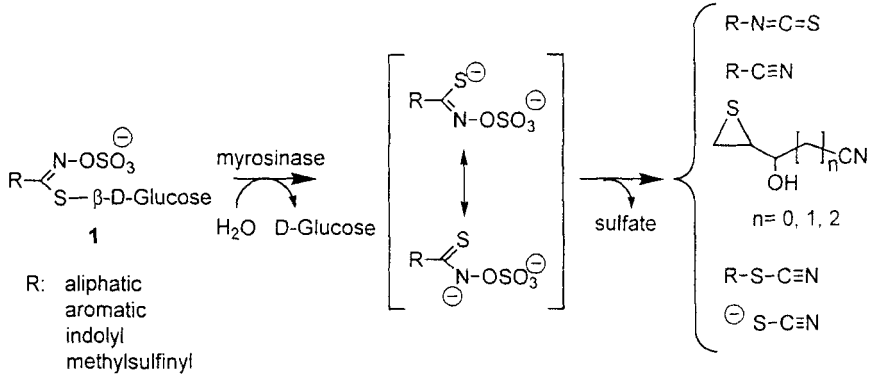
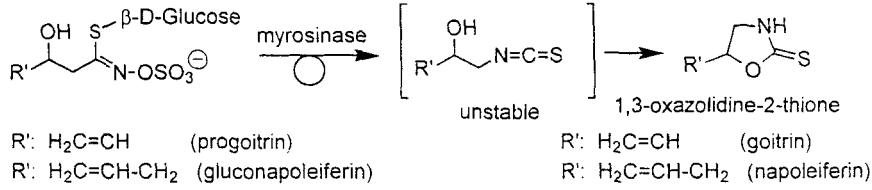
These derivatives are harmful when consumed by humans and animals [1-3] : thyroid, stomach, liver and kidney damages are known to occur in monogastric animals [4,5].



Scheme 1

Under neutral pH conditions, aliphatic glucosinolates normally lead to isothiocyanates.

Nevertheless, with a hydroxyl group β to the thioglucose moiety, the resulting compound is unstable and easily converted to a 5-alkyl-1,3-oxazolidine-2-thione (5-alkyl OZT) (Scheme 2) which presents goitrogenic properties [3-5].

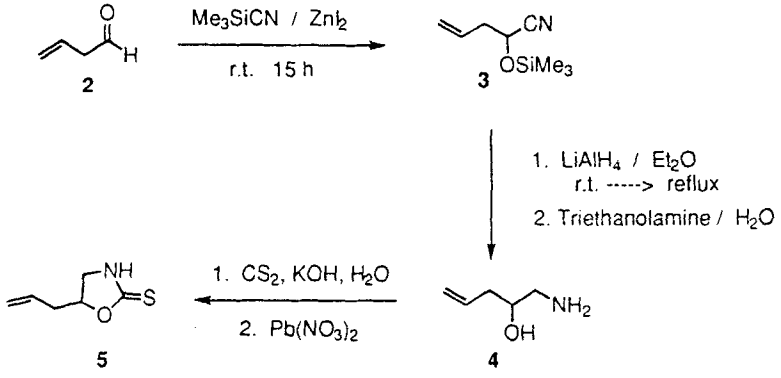


Scheme 2

In rape, two glucosinolates (progoitrin and gluconapoleiferin) belong to this category and give rise to goitrin and napoleiferin respectively, upon enzymatic

degradation. It will be of interest to get pure OZT (both goitrin and napoleiferin) in order to determine in more details their effect on animal diets.

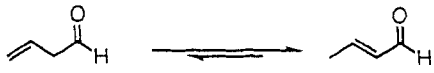
We have already described a practical synthesis of goitrin (5-vinyl OZT) [7]. In this paper we report the first preparation of napoleiferin (5-allyl OZT) based on the same reactionnal scheme (Scheme 3).



2 3 5 4

Scheme 3

The main difficulty was the synthesis of the unstable aldehyde **2**, but-3-enal. According to the literature, it has been isolated only by radical addition of acetaldehyde to acetylene in the presence of di-t-butyl peroxide under 140°C [8]. Yields and purity of the product are low. In fact aldehyde **2** is easily converted into crotonaldehyde **2'**:

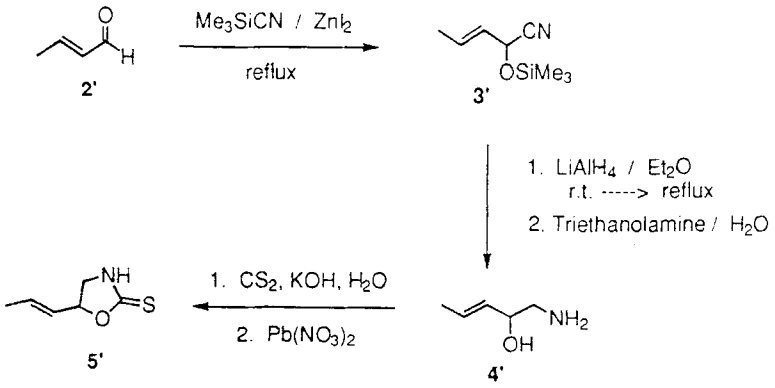


2 **2'**

Nevertheless, preparation of the corresponding acetal 1,1-diethoxybut-3-ene **6** was easily achieved in high yields [9]. Hydrolysis in strong acidic conditions [10] led to **2'**. On the other hand, with acid supported silica [11], the acetal remained

intact. In mild conditions (lithium tetrafluoroborate in aqueous acetonitrile at room temperature [12]) hydrolysis occurred to give a mixture of compounds **2** and **2'**. **2** is the main product obtained under good experimental conditions (best reaction time: 6 h). Typically the content of **2** varies from 60 to 90% depending on the extraction conditions. After 24 h **2'** was the main isolated reaction product (**2**/**2'** ~ 40/60). Aldehyde **2** was never obtained as a pure product. Anyway, we should note that commercial crotonaldehyde **2'** always contains a small amount of but-3-enal **2**. Therefore, the different reactions described in scheme 3 were performed with a mixture of **2** and **2'** (typically **2**/**2'** ~ 60/40).

Addition of trimethylsilyl cyanide to the mixtures of aldehydes **2** and **2'** in the presence of a catalytic amount of zinc iodide according to reported procedure [13] gave the adducts **3** and **3'** which can be detected by GC. NMR can be used to identify and determine the ratio of the two protected cyanohydrins (**3**/**3'** ~ 60/40): no isomerization occurred during the reaction. These compounds were reduced directly into the corresponding aminoalcohols **4** and **4'** with lithium aluminium hydride. The mixture was easily recovered by using the triethanolamine/water



Scheme 4

hydrolytic system [14]. NMR analysis gave a ratio **4**/**4'** unchanged (60/40). Finally, **4** and **4'** were converted into napoleiferin **5** and 5-prop-1-enyl OZT **5'** according to a previously reported procedure [15] with slight modifications. Using GC or HPLC analysis, the ratio of the two OZT proved to be identical and remained practically constant (**5**/**5'** ~ 60/40). Napoleiferin was eventually purified by preparative HPLC to give a pure white product. On the other hand, compound **5'** has been prepared separately from crotonaldehyde **2'** according to scheme 4.

The comparison of synthesized napoleiferin with the isolated natural product [6] from *Brassica napus* L. var. *oleifera* exhibits several differences; in particular melting points and ^{1}H-NMR spectra are quite different. A large signal about 2 ppm, appears in the ^{1}H-NMR spectrum of the natural product which was attributed by the authors to an unknown impurity. From our point of view, this signal (a very badly resolved doublet) could be attributed to the presence of a large amount of 5-prop-1-enyl OZT. As the corresponding glucosinolate (2-hydroxypent-3-enylglucosinolate) has never been described in the literature, we reasoned that the double bond mobility in napoleifeirin could be increased during the different steps involved in the natural product extraction.

Experimental

All organic reagents, zinc iodide, lithium aluminium hydride and lithium tetrafluoroborate purchased from Janssen Chimica, Aldrich Chemical Company or Fluka Chemika were of analytical grade. The other mineral products were obtained from Prolabo. Trimethylsilyl cyanide was prepared according to the literature [16]. Column chromatography was performed on Merck silica gel (60 mesh). Melting points were taken on an Electrothermal melting point apparatus and are uncorrected. Microanalyses were performed by "Service Central de

Microanalyse du CNRS" (Vernaison, France). Gas chromatography was performed on an Intersmat IGC 121C apparatus (CPSil-8 CB; 25mx0.25mm; film 0.2µm; splitless mode; FID; gas N_2); analytical HPLC was made using a Waters apparatus (column Spherisorb ODS-2; 150mmx4.6mm; particule size 5µm; UV detector 254 nm); preparative HPLC was performed on a Waters Prep LC-3000 apparatus equipped with a µBondapack C_{18} (100x25mm; particule size 10µm; UV detector 254 nm). Mass spectra were recorded on a VG model 70/70 F spectrometer. ^{1}H-NMR spectra were obtained using different apparatus (Perkin-Elmer Hitachi R-24B, Bruker WP-60 CW, Bruker AC-250); ^{13}C-NMR spectra were registered on a Bruker AC-250 spectrometer. All NMR spectra are reported in δ ppm units; the solvent and the internal standard are given in each case.

1,1-Diethoxybut-3-ene 6

Compound **6** was prepared from anhydrous acetone (100 ml), yellow mercuric oxide (3 g, 14 mmoles), boron trifluoride etherate (0.35 g, 2.4 mmoles) and 1-ethoxyethylene (300 g, 4.16 moles) according to the literature [10]. After elimination of unreacted products, the core was distilled twice under reduced pressure to give **6** (98 g, 68%) as a pale yellow liquid, bp: 69-70 °C/56 Torr (lit[17], bp: 70 °C/56 Torr); ^{1}H-NMR (carbon tetrachloride, TMS): δ=1.1 (t, 6H, $C\underline{H}_3$-CH_2); 2.3 (dd, 2H, $C\underline{H}_2$-CH); 3.2-3.8 (m, 4H, 0-$C\underline{H}_2$); 4.4 (t, 1H, $C\underline{H}$-O); 4.8-5.2 (n, 2H, $C\underline{H}_2$=CH); 5.4-6.2 (m, 1H, CH_2=$C\underline{H}$).

But-3-enal 2 and but-2-enal 2'

A solution of lithium tetrafluoroborate (937 mg, 10 mmoles) in 2% aqueous acetonitrile (10 ml) was slowly added under magnetic stirring to 1,1-diethoxy-but-3-ene **6** (1.440 mg, 10 mmoles). The flask in which the lithium tetrafluoroborate solution was prepared was rinsed with 2% aqueous acetonitrile

(10 ml). (The acetal concentration is 0.5 mole L^{-1}). Stirring was continued for 6 hours. The mixture was neutralized by sodium hydrogenocarbonate and the aqueous layer was extracted four times with ether (1x20 ml and 3x10 ml). The organic phase was dried (magnesium sulfate), filtered and moderately concentrated at atmospheric pressure. Heating or total elimination of the solvent diminishes the yield and purity of the product. The but-3-enal purity is not reproducible and can vary from 60 to 90%. The **2/2'** ratio was determined by ^{1}H-NMR in the 9.0-10 ppm region . The aldehydic proton of **2** is a triplet (δ=9.7ppm, J=1.5Hz) and the aldehydic proton of **2'** is a doublet (δ=9.5 ppm, J=7.5 Hz).

2-(Trimethylsilyloxy)pent-4-enenitrile 3 and 2-(Trimethylsilyloxy)pent-3~enenitrile 3'

A mixture of butenals (**2/2'** ~ 60/40) and anhydrous ether, trimethylsilyl cyanide (7.0 g, 710 mmoles) and a minute amount of zinc iodide (5 mg) was maintained at ambient temperature under magnetic stirring for 15 hours. After elimination of unreacted products *in vacuo*, the solution was distilled under reduced pressure to give a mixture of **3** and **3'** (3.1 g, yield 26%) as a light yellow liquid, bp: 40-53°C/0.2 Torr; the repartition of both isomers was made by ^{1}H-NMR [**3'** shows a "doublet" at δ 1.9 ppm ($\underline{CH_3}$-CH=) and **3** a "triplet" at δ 2.7 ppm (=CH-$\underline{CH_2}$ -CH)]: **3/3'** ~ 60/40.

1-Aminopent-4-ene-2-ol 4 and 1-aminopent-3-ene-2-ol 4'

From the reduction of **3** and **3'** (7.3 g, 43 mmoles) by lithium aluminium hydride performed in the same manner as 1-aminobut-3-ene-2-ol [7], a mixture of **4** and **4'** was isolated (4 g, yield 92%). The ratio of both isomers (**4/4'**~60/40) was determined by ^{1}H-NMR (based on the integration of the signals corresponding to hydrogens α to the hydroxyl groups).

5-Allyl-1,3-oxazolidine-2-thione 5 and 5-prop-1-enyl-1,3-oxazolidine-2~ thione 5'

A mixture of the two aminoalcohols **4** and **4'** (4 g, 39 mmoles) was treated similarly as goitrin [7] to give a crude product (3.2 g) purified on silica gel (pentane/ethyl acetate from 4/1 to 1/1). Both OZT were obtained (1.9 g, yield 37%) in the ratio **5/5'** ~ 60/40; the calculation was based on the integration of the signal given by the allylic methylene of napoleiferin **5** (a kind of triplet δ 2.5 ppm) and the signal given by the methyl group of 5-prop-1-enyl-1,3~ oxazolidine-2-thione **5'** (doublet δ 1.7 ppm).

5-Allyl-1,3-oxazolidine-2-thione 5 (napoleiferin)

Compounds **5** and **5'** were separated by preparative HPLC (acetonitrile/water 4/96). After lyophilisation, white crystals of pure napoleiferin were obtained (722 mg, yield 14%; overall yield from 1,1-diethoxybut-3-ene **6** ~ 5%). mp: 54 °C (lit [6]: 60-61 °C). ^{1}H-NMR ($CDCl_3$, TMS) : δ = 2.42-2.62 ppm (m, 2H, CH_2=CH-C$\underline{H_2}$); 3.41-3.48 ppm (m, 1H, C$\underline{H_2}$-NH); 3.76-3.83 ppm (m, 1H, C$\underline{H_2}$-NH); 4.91-5.02 ppm (m, 1H, C$\underline{H}$-O); 5.13-5.19 ppm (m, 2H, C$\underline{H_2}$=CH); 5.63-5.79 ppm (m, 1H, CH_2=C$\underline{H}$); 8.45 ppm (s, 1H, N$\underline{H}$). ^{13}C-NMR ($CDCl_3$) : δ = 189.3 ppm (C_2); 48.3 ppm (C_4); 82.2 ppm (C_5); 38.3 ppm (C_6); 130.6 ppm (C_7); 119.9 ppm (C_8). MS (EI, 70 eV): m/z (relative abundance %) 143 (Molecular ion, 100); 102 (24.5); 82 (26.3); 74 (17.2); 68 (16.8); 67 (26.1); 56 (9.7); 54 (30.0); 41 (39.3); 39 (30.7).

Anal. Calcd. for C_6H_9NOS: C, 50.32; H, 6.33; N, 9.78; S, 22.39. Found: C, 50.13; H, 6.19; N, 9.58; S, 22.02.

2-[(Trimethylsilyl)oxy]pent-3-enenitrile 3'

Compound **3'** (15 g, yield 62%) was obtained from crotonaldehyde (10 g,

143 mmoles) similarly as the **3** and **3'** mixture. Nevertheless the solution was maintained under reflux until the total disappearence of crotonaldehyde. bp: 78 °C/4 Torr (lit [17], bp 79 °C/3 Torr). n_D^{20} = 1.4239. ^{1}H-NMR (CCl_4, benzene): δ = 0.4 ppm (s, 9H, $SiMe_3$); 1.9 ppm (d, 3H, CH_3-CH=); 4.9 ppm (d, 1H, CH-OSi); 5.2-6.3 ppm (m, 2H, -CH=CH-).

1-Amino-2-hydroxypent-3-ene 4'

Compound **4'** (5.7 g, yield 63%) was prepared from 2[(trimethylsilyl)oxy]pent-3-enenitrile **3'** (15 g, 90 mmoles) in the same manner as the mixture of **4** and **4'**. bp: 82 °C/5 Torr. ^{1}H-NMR (CCl_4, TMS): δ = 1.6 ppm (d, 3H, CH_3-CH=); 2.4 ppm (m, 2H, CH_2-NH_2; this signal gives a doublet with D_2O); 2.6 ppm (s, 3H, OH, NH_2; this signal disappears in the presence of D_2O); 3.7 ppm (dd, 1H, CHOH); 5.0-5.8 ppm (m, 2H, -CH=CH-).

5-prop-1-enyl-1,3-oxazolidine-2-thione 5'

Crude product **5'** was obtained from 1-amino-2-hydroxypent-3-ene **4'** (5.7 g, 56 mmoles) in the same manner as the mixture of **5** and **5'**. After purification on silica gel (pentane/ethyl acetate 1/1) a white solid was isolated (1.16 g, yield 20%). mp: 94 °C. ^{1}H-NMR ($CDCl_3$, TMS): δ = 1.71 ppm (d, 3H, CH_3); 3.42-3.49 ppm (m, 1H, CH-CH_2-N); 3.81-3.89 ppm (m, 1H, CH-CH_2-N); 5.55-5.95 ppm (m, 3H, -CH=CH-CH); 8.48 ppm (s, 1H, NH). ^{13}C-NMR ($CDCl_3$): δ = 189.4 ppm (C_2); 49.5 ppm (C_4); 84.2 ppm (C_5); 134.1 ppm (C_6); 126.4 ppm (C_7); 17.9 ppm (C_8).

Anal. Calcd. for C_6H_9NOS: C, 50.32; H, 6.33; N, 9.78; S, 22.39. Found: C, 50.26; H, 6.22; N, 9.62; S, 22.21.

References

1. Tookey, H.L., Van Etten, C.H. and Daxenbichler, M.E. "*Toxic Constituents of Plant Foodstuffs*", 2nd ed., Liener I.E. ed., Academic Press, New York, 1980, Chap.4.
2. Van Etten, C.H. and Tookey, H.L."*CRC Handbook of Naturally Occurring Food Toxicants*", CRC Series in Nutrition and Food, Rechcigl M. Jr ed., CRC Press Inc., Boca Raton, Florida, 1983, p. 15.
3. Fenwick, G.R., Heaney, R.K. and Mullin, W.J. *CRC Crit. Rev. Food Sci. Nutr.* **1983**, *18*, 123.
4. Vermorel, M., Heaney, R.K. and Fenwick, G.R. *J. Sci. Food Agric.* **1988**, *44*, 321.
5. Vermorel, M., Davicco, M.J. and Evrard, J. *Reprod. Nutr. Dev.* **1987**, *27*, 57.
6. Tapper, B.A. and Mc Gibbon, D.B. *Phytochemistry* **1967**, *6*, 749.
7. Gardrat, C., Latxague, L. and Picard, J.P. *J. Heterocyclic Chem.* **1990**, *27*, 811.
8. Mekhtiev, S.D., Mamedov, M.K., Aliev, V.S., Sultanov, N.T., Guseinov, N.M., Mamedov, F.A., Popova, T.P. and Aliev, M.I. SSSR Patent 292,947 (*Chem. Abstr.* **1971**, *75*, 5250q). Sultanov, N.T., Abilov, A.G., Mekhtiev, S.D. and Karaev, G.K. *Azerb. Neft. Khoz.* **1973**, *53*, 36.
9. Makin, S.M., Raifeld, Yu.E., Limanova, O.V. and Chavrygina, O.A. *Zhur. Org. Khim.* **1979**, *15*, 1848.
10. Makin, S.M. and Kruptov, B.K. *Zhur. Obsch. Khim.* **1960**, *30*, 3276.
11. Huet, F., Lechevallier, A., Pellet, M. and Conia, J.M. *Synthesis* **1978** , 63.
12. Lipshutz, B.H. and Harvey, D.F. *Synth. Commun.* **1982**, *12*, 267.
13. Evans, D.A., Truesdale, L.K. and Carroll, G.L. *J. Chem. Soc., Chem. Commun.* **1973**, 55. Evans, D.A., Carroll, G.L. and Truesdale, L.K. *J. Org. Chem.* **1974**, *39*, 914.
14. Powell, J., James, N. and Smith, S.J. *Synthesis* **1986**, 338.
15. Ettlinger, M.G. *J. Am. Chem. Soc.* **1950**, *72*, 4792.
16. Picard, J.P., Elyusufi, A.A., Calas, R., Dunoguès, J. and Duffaut, N. *Organometallics*

1984, *3*, 1660.

17. Duboudin, F., Cazeau, P., Moulines, F. and Laporte, O. *Synthesis* **1982**, 212.

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