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Carbohydrate Research 335 (2001) 147–150

CARBOHYDRATE RESEARCH

Rapid Communication

Synthesis of hydantocidin and *C*-2-thioxo-hydantocidin

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Received 23 July 2001; accepted 23 August 2001

Abstract

Hydantocidin, a naturally occurring strong herbicide, was synthesized in an overall yield of 35.2%, with the accompanying 1′-*epi*-hydantocidin in overall 9.6% yield from 2,3-*O*-isopropylidene-D-ribono-1,4-lactone. *C*-2-thioxo-hydantocidin and its spiro-epimer were also synthesized in an overall yield of 14.4% and 8.5%, respectively.

Keywords: Hydantocidin; Herbicide; Synthesis of spiro-hydantoin

Together with the explosive increase in the world population, deficiency of provisions, environmental destruction and pollution, and global warming have become serious problems. Means for grain production to maintain this large population have come under increased development. One aspect is the use of herbicides. Glyphosate has become one of the most popular herbicides in the world. However, glyphosate-resistant weeds have been reported recently. In addition, proteins produced by grain plants recombinated by a glyphosate-resistant gene are a cause for concern because of the awareness of the existence of pathogenic proteins.

Hydantocidin produced from *Streptomyces hygroscopicus*,[1] the first naturally occurring spiroribofuranose having strong herbicidal activity toward annual, biennial and perennial weeds by action as an adenylosuccinate synthetase inhibitor,[2] without showing toxicity to microorganisms and animals, and without remaining for a long period in the soil, may be used in the near future as a potential herbicide against glyphosate-resistant weeds. However, the high cost of hydantocidin production, whether by fermentation or by total synthesis,[3] has made its use as a herbicide impracticable. Therefore, economical production of hydantocidin is being sought. At this time, the author has accomplished a fairly good overall yield for hydantocidin, that is, hydantocidin (**9**) was synthesized in overall 35.2% yield, accompanied by 1′-*epi*-hydantocidin (**9′**) in overall 9.6% yield from 2,3-*O*-isopropylidene-D-ribono-1,4-lactone (**1**). The synthetic route (Scheme 1) is reported herein.

The starting material 2,3-*O*-isopropylidene-D-ribono-1,4-lactone (**1**), was converted to its 5-*O*-benzyl ether **2** or 5-*O*-(*p*-methoxybenzyl) ether (**10**) in 95% or 77% yield, respectively, by treatment with benzyl bromide or *p*-methoxybenzyl chloride using NaH as a base.

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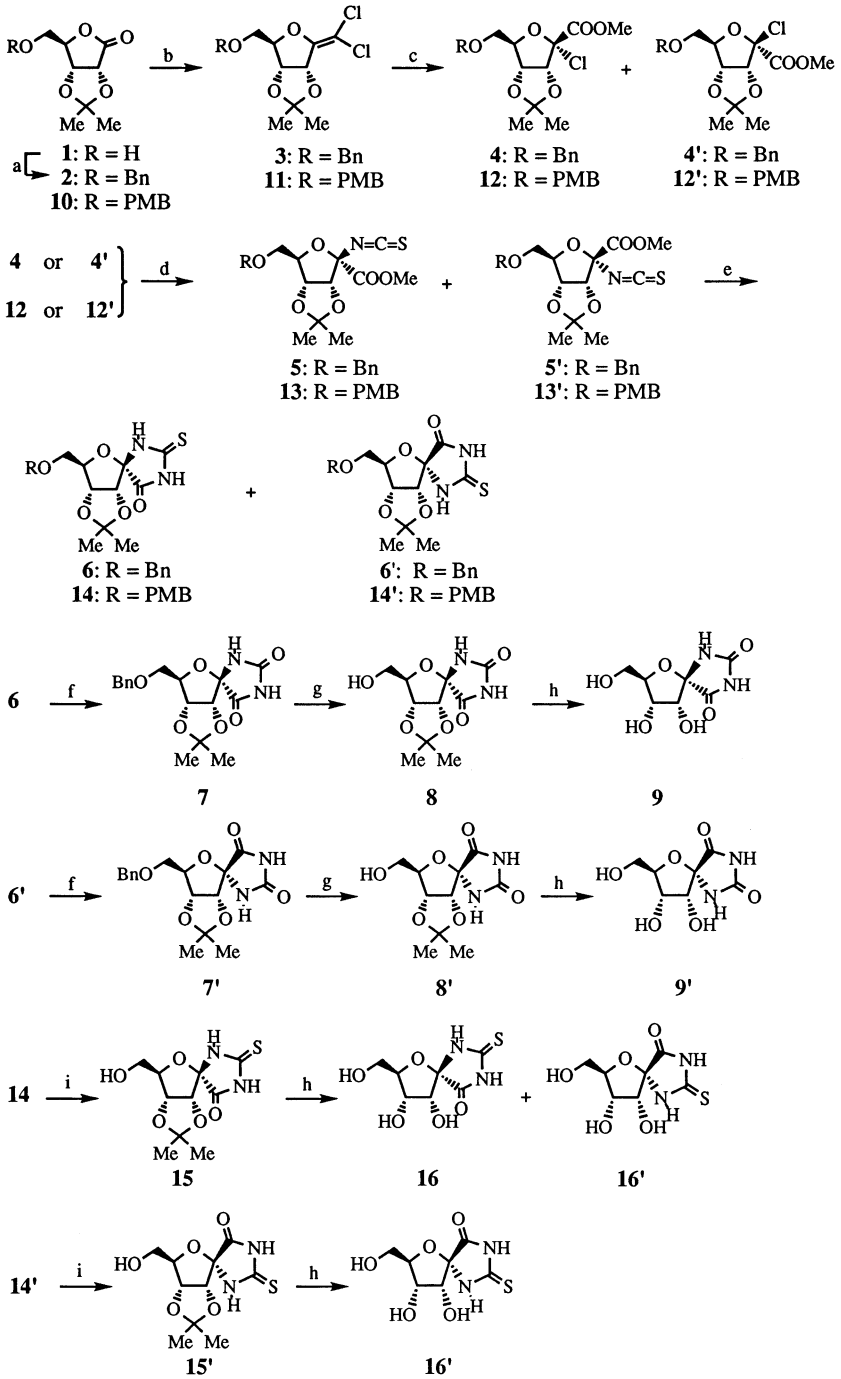
0008-6215/01/$ - see front matter
PII: S0008-6215(01)00239-7



Scheme 1. Reagents and conditions: Bn = benzyl; PMB = *p*-methoxybenzyl; (a) NaH, BnBr or PMB-Cl, DMF, 0 °C ~ rt, 95% or 77%, respectively; (b) $CBrCl_3$, $(Me_2N)_3P$, CH_2Cl_2, −78 ~ +24 °C, 16 h, 86% or 95%, respectively. ; (c) *m*-CPBA, MeOH, CH_2Cl_2, 24 °C, 16 h, **4** (54%) and **4′** (14%), or **12** (54%) and **12′** (13%); (d) KNCS, DMF 80 °C, 16 h, a 4:1 mixture of **5** and **5′** (83%) from **4**, a 5:2 mixture of **5** and **5′** (72%) from **4′**; a 5:1 mixture of **13** and **13′** (73%) from **12**, and a 3:1 mixture of **13** and **13′** (72%) from **12′**; (e) NH_3, MeOH, rt 2 h, quant; (f) 30% H_2O_2, $NaHCO_3$, $MeCN–H_2O$, rt, 15 min, quant; (g) H_2, Pd/C, EtOAc, rt, 15 min, quant; (h) $CF_3COOH–H_2O$, 0 °C, 30 min, **9** and **9′**, quant: $CF_3COOH–H_2O$ (1:3), −5 °C, 16 h, **16** (61%) and **16′** (16%) from **15**, and **16′** (94%) from **15′**; (i) PhSH, $SnCl_4$, CH_2Cl_2, −78 °C, 30 min **15** (81%) and recovery of **14** (6%); **15′** (76%) and recovery of **14′** (13%).

Treatment of **2** with CCl_3Br using $(Me_2N)_3P$ (HMPT) as a base gave dichloroolefin **3**,[4] which was further converted to methyl α-chlorourosonates **4** and **4′** in 68% yield as a 4:1 diastereomeric mixture by treatment with *m*-chloroperoxybenzoic acid according to Chapleur's procedure.[5] Compound **10** was also converted to **12** and **12′** in 67% yield as a

4:1 diastereomeric mixture via compound **11** by the same procedure. Treatment of **4′** at 80 °C for 1 h in DMF gave a 3:1 mixture of **4** and **4′**. Therefore, compound **4** is more thermodynamically stable than **4′**. Thus, at high temperature, compound **4′** gradually changed to **4** until equilibration was reached (Scheme 1).

After separation of **4** and **4′** or **12** and **12′** chromatographically, treatment of **4** with potassium thiocyanate at 80 °C for 16 h in DMF gave a 4:1 inseparable mixture of **5** and **5′** in 83% yield. The same treatment of compounds **4′**, **12**, and **12′** gave a 5:2 inseparable mixture of **5** and **5′** in 72% yield from **4′**, a 5:1 inseparable mixture of **13** and **13′** in 73% yield from **12**, and a 3:1 inseparable mixture of **13** and **13′** in 72% yield from **12′**, respectively.

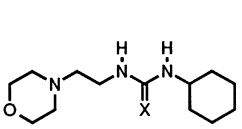
Treatment of the 4:1 mixture of **5** and **5′** with NH_3 in MeOH afforded a 4:1 mixture of spiro-thiohydantoins **6** and **6′** in quantitative yield according to the ratio of the starting **5** and **5′**. The same procedure for both compounds **13** and **13′** gave spiro compounds **14** and **14′**, respectively, in quantitative yield.

After chromatographic separation of **6** and **6′**, treatment of each compound with 30% H_2O_2 and $NaHCO_3$ in 3:2 $MeCN–H_2O$ yielded **7** and **7′**, respectively, in quantitative yield.[6] This procedure was also applicable for the oxidation of thiourea **17**, thiohydantoin **19** and cyclic thiocarbamate **21**[7] to give a water soluble urea **18**, hydantoin **20**, and cyclic carbonate **22**, respectively (Table 1). Deprotection of the benzyl ether of **7** and **7′** by means of hydrogenolysis using Pd/C as a catalyst quantitatively gave **8** and **8′**, respectively. Finally, the *O*-isopropylidene protecting groups of **8** and **8′** were quantitatively cleaved by treatment with 3:1 $CF_3COOH–H_2O$ at 0 °C for 30 min according to a previously reported procedure[3f] to give **9** and **9′** (1′-*epi*-hydantocidin having still strong herbicidal activity according to Ref. 8), respectively. Thus, hydantocidin (**9**) was synthesized in overall 35.2% yield accompanying 1′-*epi*-hydantocidin (**9′**) in overall 9.6% yield from 2,3-*O*-isopropylidene-D-ribono-1,4-lactone (**1**).

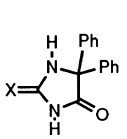
On the other hand, treatment of solutions of **14** and **14′** in CH_2Cl_2 with PhSH and $SnCl_4$, at −78 °C under nitrogen gave **15** and **15′** in 81% and 76% yields, respectively, along with the recovery of **14** (6%) and **14′** (13%).[9] Finally, the protecting *O*-isopropylidene group of **15** was cleaved by treatment with 3:1 $CF_3COOH–H_2O$ at 0 °C for 30 min according to a previously reported procedure[3f] to give a mixture of **16** (61%) and **16′** (16%). However, the same treatment of **15′** gave **16′** in 94% yield. It is reported that both compound **16** and **16′** are comparable with hydantocidin **9** in herbicidal activity toward many different types of weeds.[7] As a result, *C*-2-thioxo-hydantocidin (**16**) and its spiro epimer **16′** were synthesized in overall yields of 14.4% and 8.5%, respectively.

Thus, hydantocidin (**9**), 1′-*epi*-hydantocidin (**9′**), *C*-2-thioxo-hydantocidin (**16**), and 1′-*epi*-*C*-2-thioxo-hydantocidin (**16′**) were synthesized from D-ribono-1,4-lactone via corresponding isothiocyanates **5**, **5′**, **13**, and **13′**[†].

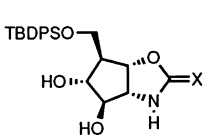
Table 1
Oxidation of thiourea (**17**), thiohydantoin (**19**), and cyclic thiocarbamate (**21**) with 30% H_2O_2 in 3:2 1 M aq $NaHCO_3$ at 24 °C



17: X = S
18: X = O



19: X = S
20: X = O



21: X = S
22: X = O

Entry	Substrate	Time (min)	Product	Yield (%)
1	**17**	4 [a]	**18**	57
2	**19**	30	**20**	100
3	**21**	20	**22**	96

[a] Prolonged reaction time causes production of the morpholine *N*-oxide of **18**.

Acknowledgements

I thank Dr. Shigeru Mio for helpful advice and discussions.

[†] All new compounds were characterized by IR, ^1H NMR, MS and elemental analysis.

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