Tetrahedron Letters,Vol.25,No.5,pp 487-490,1984 0040-4039/84 $3.00 + .00
Printed in Great Britain

A SHORT, EFFICIENT TOTAL SYNTHESIS OF (±) ACIVICIN AND (±) BROMO-ACIVICIN

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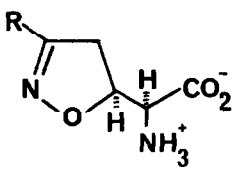
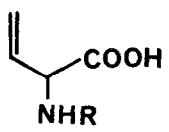
Abstract: A practical approach to the synthesis of (±) acivicin (1) and (±) bromo-acivicin (6) has been developed. It centers on the synthesis of alkene 10 by a thermal [3,3] sigmatropic rearrangement of trichloroimidate 9.

The total synthesis[1] of antitumor, antimetabolite (αS,5S)α-amino-3-chloro-4,5-dihydro-5-isoxazole acetic acid (acivicin, 1) has been a subject of considerable interest since its isolation from fermentation broth of Streptomyces sviceus by the Upjohn group.[2] The most direct and facile synthesis of 1 known to date is that of Wade and co-workers, who employed a (3+2)cycloaddition reaction between N-phthalimido-L-vinylglycine 2 and chloronitrile oxide 3 to construct the 3-chloroisoxazoline ring. Earlier, Hagedorn and co-workers,[3] employing the same stragety with vinylglycine (4) and bromonitrile oxide (5) reported the synthesis of the unnatural bromo analog 6 (bromo-acivicin). It is claimed[3] that 1 and 6 have identical antitumor properties. A major prerequisite for the commercial scale synthesis of either 1 or 6 via the 1,3-dipolar cycloaddition approach is the accessibility of vinylglycine (4), which also has held a long-standing interest[4] among synthetic chemists because of its biological importance.[5] In the present communication, we wish to report the results of

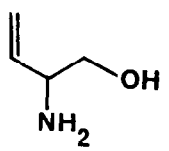


1 R = Cl
6 R = Br



2 R = Pht
4 R = H

3 X = Cl
5 X = Br



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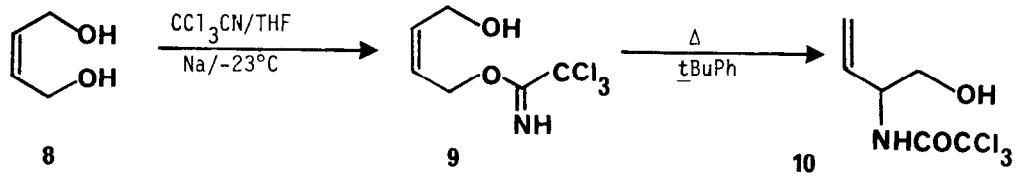
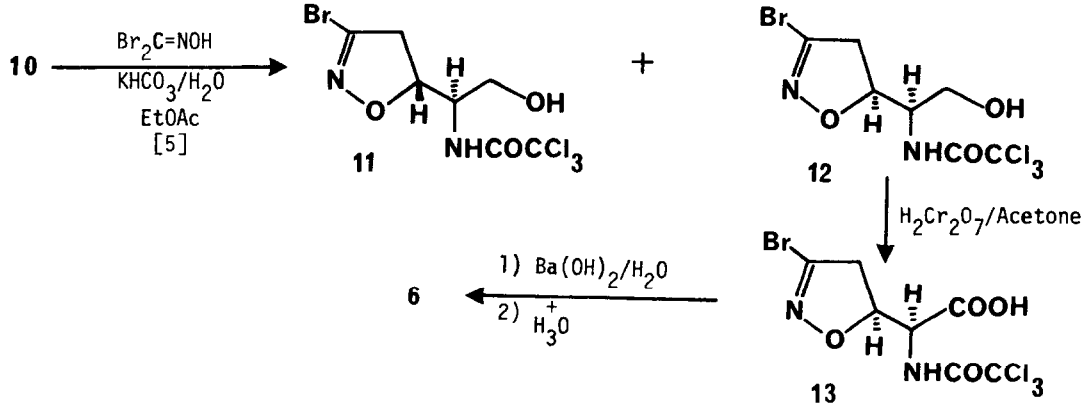
our investigations targeted towards the total synthesis of racemic 1 and 6.

At the outset, we realized that in order to employ the 1,3-dipolar cycloaddition methodology to synthesize 1 and 6, we would require a vinyl glycine equivalent. Consequently, our prime synthetic target was 2-amino-3-butene-1-ol (7). Its reported synthesis[6] from butadiene monoepoxide is inefficient and hazardous and as a result an alternate synthesis was sought. It is well documented[7] in the literature that allylic trichloroacetimidic esters undergo facile [3,3]sigmatropic rearrangement thermally to yield an allylic transposed trichloroacetamide. Thus, starting from commercial, cis-2-buten 1,4-diol (8), the monotrichloroacetimidate (9)[8] was readily obtained as a colorless liquid (60%, b.p. 88-102°/0.2 mm Hg) by treatment with trichloroacetonitrile[9] (1 equivalent) in tetrahydrofuran at -23°C in the presence of catalytic amount of sodium. Compound 9 upon refluxing in tert-butyl benzene for ∿1 hr. underwent, smoothly, a [3,3]sigmatropic rearrangement to afford the vinylglycine synthon 10 (84%, m.p. 38°C).

At this stage, the assembly of bromo-acivicin (6) from 10 proceeded routinely via the general route of Hagedorn et al.[3] Thus, treatment of 10 with bromonitrile oxide 5 (3 equiv.)

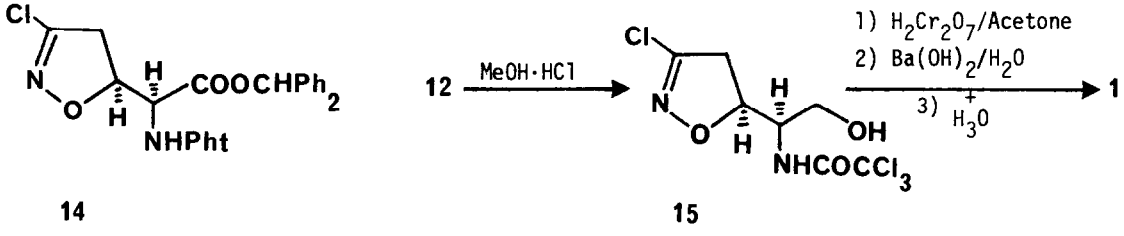


generated in situ from dibromoformaldoxime[10] in ethyl acetate containing excess of $KHCO_3$ and trace amounts of water afforded a 3:2 mixture of cycloadducts 11 and 12 respectively. The undesired threo isomer 11 (m.p. 164-165°C) was quantitatively removed from the mixture by fractional crystallization from chloroform.



The erythro isomer 12 (oil), when subjected to Jones oxidation ($H_2Cr_2O_7$/acetone), afforded crystalline N-trichloroacetyl bromo-acivicin (13) (75%, m.p. 155-157°C). Removal of the trichloroacetyl group in 13 was accomplished by treatment with barium hydroxide and upon neutralization, bromo-acivicin was obtained as a crystalline solid (λ_{max} (H_2O)=214 mm).

Synthesis of acivicin (1) from either 12 or 13 required the substitution of bromine with chlorine. The reverse situation was encountered by Kelly and co-workers,[1a] who during the deblocking of the benzhydryl ester 14 with HBr-nitromethane saw a rapid and complete substitution of the ring chlorine by bromine. Interestingly in our case, treatment of bromo-alcohol 12 with methanolic-HCl (reflux 1 hr) afforded the chloro-alcohol 15 (50%, syrup), which upon Jones' oxidation followed by deprotection of the trichloroacetyl group afforded racemic acivicin (1) (66%, λ_{max}=216). The synthetic, racemic 1 was spectrally (uv, ^{1}H NMR) indistinguishable from the natural product.[11]



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The process described here because of its procedural simplicity and the use of inexpensive chemicals holds considerable promise for the commercial scale synthesis of either acivicin (six steps) or bromo-acivicin (five steps).

Acknowledgement: Support by the National Institute of Health (Grant No. NO1-CM87180) is gratefully acknowledged.

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10. I. DePaolini, Gazz. Chim. Ital., 60, 700 (1930). The following modified one pot process was developed to prepare large quantities (∿0.5 kg) of this material. To a stirred solution of glyoxylic acid (500 g) in water (∿4 l) was added hydroxylamine hydrochloride (470 g) and the solution was stirred for 24 hr. Sodium bicarbonate (1176 g) was added carefully followed by methylene chloride (5 l). To the two-phase well stirred mixture at 6°C was added bromine (482 ml in 2.5 l CH_2Cl_2) at such a rate that the temperature of the reaction mixture did not rise above 10°C. Upon completion of the addition of bromine, the solution was further stirred (3 hr), cooled and the organic layer separated. The aqueous layer was extracted with methylene chloride (5 l). The combined organic extract was dried (anhyd. $MgSO_4$), filtered and evaporated. The residue, upon crystallization from Skellysolve B afforded the title compound (500 g, m.p. 65-66°C) as a crystalline, colorless solid.
11. Natural acivicn was provided by the NCI. The synthetic (±)1 and (±)6 showed comparable in vivo antitumor activity in the same L1210 murine leukemia test to the natural product at equivalent doses e:g at 8 mg/kg dose T/C (%) for natural acivicin = 192, T/C (%) for (±)1 = 185; T/C (%) for (±)6 = 169.

(Received in USA 17 October 1983)