Table I. Bond Distances (Å) and Bond Angles (deg) for the $CH_3O^-\cdot 6H_2O$ Unit in **1** and **2**

	structure	
	1	**2**
H_3C-O	1.38 (1)	1.33 (2)
$H_3CO\cdots(H)OH(Ow4)$	2.721 (9)	2.80 (1)
$H_3CO\cdots OH_2(Ow3)$	2.95 (1)	2.95 (1)
$C_{me}-O_{me}-O(w4)$	126 (1)	128.8 (9)
$C_{me}-O_{me}-O(w3)$	91.0 (7)	91 (1)

$(PhC(O)=N(O))_3]\cdot I\cdot CH_3O\cdot 3CH_3OH\cdot 10^1/_2H_2O$ (**1**) and in the isostructural $Na_5[Co(PhC(O)=N(O))_3]\cdot Br\cdot CH_3O\cdot 3CH_3OH\cdot 10^1/_2H_2O$ (**2**).[7]

Compound **1** was originally prepared by Raymond et al. and was formulated as "$Na_3[Cr(PhC(O)=N(O))_3]\cdot NaI\cdot NaOH\cdot 9H_2O\cdot 3CH_3OH\cdot C_2H_5OH$".[8] Our attention was drawn to this compound in the course of a reexamination of single-crystal structures in which the existence of a distinct hydrated hydroxide ion had been claimed.

The presence of an OH^- ion in **1**, rather than an H_2O molecule of crystallization, was proposed in order to account for the mismatch of charges (3- for the chromium complex, 1- for the iodide, and 5+ for the sodium ions in each formula unit).[8] This compound was originally prepared by dissolving $[Cr(PhC(O)=NH(O))_3]$ in an aqueous solution of NaOH in the presence of iodide ions, ethanol, and methanol.[8] We have shown that the presence of the ethanol is not essential and that crystals of **1** are obtained with or without ethanol. The concentrations of the OH^- ion and of the methanol in the solution in which the crystals are grown are 4.4 and 7.4 M, respectively, and the calculated CH_3O^- ion concentration is about 1.8 M.

A crystal of **1**, prepared in our laboratory, was subjected to a low-temperature X-ray analysis and the results call for a revision of the original formula.[9] First, the assignment of the oxygen atom O(W3) as a hydroxide ion is erroneous since it resides in a 12-fold general position and hence exists in a 3:1 ratio of OH^-/Cr rather than 1:1. Since all the hydrogen atoms in **1** were located from the difference Fourier map in our study it is obvious from the hydrogen bonds scheme that O(W3) is a water molecule rather than an OH^- ion. Second, the "ethanol" molecule of crystallization, that was found residing on the threefold axis[8] is, in fact, a methoxide ion, CH_3O^-, hydrogen bonded to three water molecules and surrounded by three additional ones as shown in Figure 1.

The distances of the three (symmetry related) hydrogen bonds, $H_3CO\cdots O(W3)$ in **1** and **2** and of the three $H_3CO\cdots O(W4)$ contacts are given in Table I. Both O(W3) and O(W4) are part of the hydration sphere of the CH_3O^- anion and of some of the sodium cations. The positive charge of the 20 Na^+ cations in the cell is balanced by the negative charge of the four CH_3O^-, four $[Cr(PHC(O)=N(O))_3]^{3-}$, and four iodide anions.

Several theoretical studies on the hydrated methoxide ion in the gas phase were performed but most of them dealt with the monohydrate, $CH_3O^-\cdot H_2O$.[3,5a] In some of these calculations, the proposed H_3C-O^- distances are in the range of 1.33-1.37 Å and they resemble the values found in the crystals of **1** and **2** (Table I). In previous structural studies of simple salts of the methoxide ion such as $M(CH_3O)_2$ (M = Ca, Sr, Ba), the H_3C-O distances were in the range of 1.39-1.40 Å.[10]

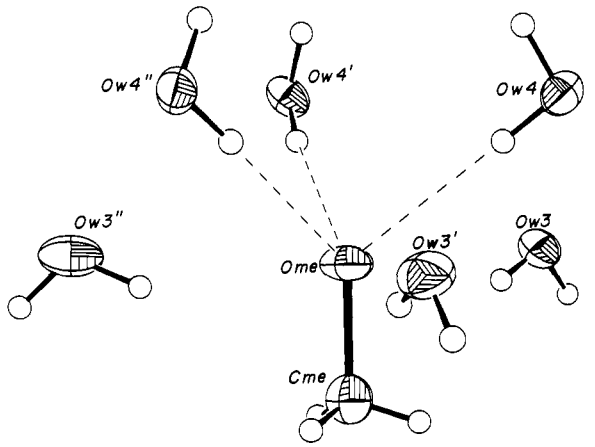

Figure 1. Structure of $CH_3O^-\cdot 6H_2O$. The atoms O_{me} and C_{me} reside on a crystallographic threefold axis. The dotted lines represent the hydrogen bonding between the CH_3O^- ion and the water molecules, O(W4)-O(W4)". All hydrogen atoms have been located from the difference Fouriers.

The calculated O-O distances of the $H_3CO\cdots(H)OH$ hydrogen bond are in the range of 2.57-2.64 Å,[3,5a] and they differ significantly from the corresponding distances found in the crystals of **1** and **2** (Table I). These variations are probably the result of the difference between the hydration number in the crystal and those in the theoretical calculations as well as of the interactions with the counterions in the solid.

Jorgensen et al. estimated the average solvation number of CH_3O^- in methanol and of OH^- in H_2O to be about 5.[11] This work shows that in the solid state, the CH_3O^- ion is surrounded by six water molecules, in a trigonal symmetry, and it is not unlikely that a similar hydration system exists in the aqueous solution of CH_3O^-.

Supplementary Material Available: Tables of atomic positional parameters for **1** and **2** and a structure of the $CH_3O^-\cdot 6H_2O$ system and the nearest sodium cations (4 pages). Ordering information is given on any current masthead page.

(7) Compound **2** was prepared by reacting $CoCl_2\cdot 6H_2O$ (0.5 g) and potassium benzohydroxamate (1.1 g) in methanol (25 mL). The pink slurry of $[Co(PhC(O)=NH(O))_3]$ was added to a hot solution of NaOH (15 g) and NaBr (5 g) in H_2O(60 mL). Green crystals were obtained after several hours. The crystals are trigonal, space group $P\bar{3}c1$, a = 13.541 (2) Å and c = 25.981 (3) Å. Anal. Calcd for $BrCoNa_5O_{20.5}N_3C_{25}H_{48}$: C, 30.88; H, 4.98; N, 4.32. Found: C, 30.14; H, 4.83; N, 4.22.

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(9) Data were collected at -90 °C. The green-purple crystals belong to space group $P\bar{3}c1$ with a = 13.583 (1) Å, c = 26.170 (2) Å, V = 4181 (1) Å^3, and Z = 4. The structure was refined by least-squares methods using 2459 reflections with $I > 3\sigma(I)$ to a conventional R factor of 0.057.

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A Total Synthesis of Acivicin

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Acivicin (AT-125) (**1**) is an antimetabolite antibiotic, produced by *Streptomyces sviceus*, for which the isolation and structure elucidation were reported by Martin et al.[1] in 1973. The antitumor properties associated with this compound are a consequence of irreversible inhibition of a number of glutamine-requiring enzymes involved in the de novo biosynthesis of purine and pyrimidine nucleotides.[2] Initial phase II clinical trials have indicated that acivicin may be useful in the treatment of non-small cell lung cancer;[3] additional clinical trials are ongoing and underscore the

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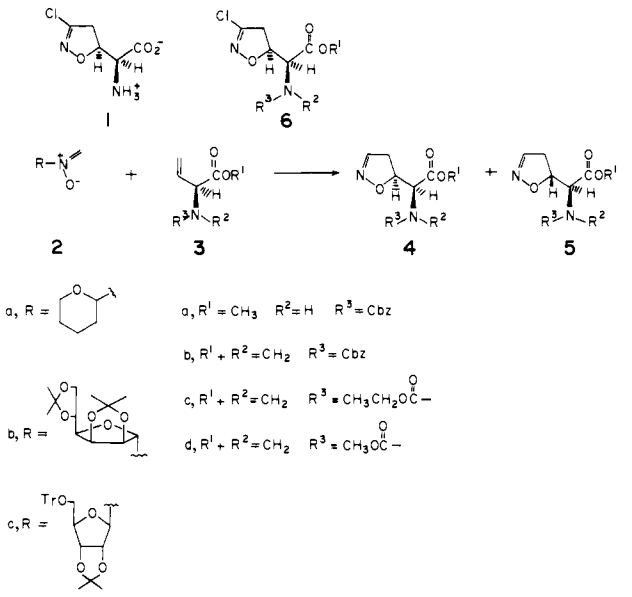
Scheme I



importance of this compound as a synthetic target. Not surprisingly, several total syntheses of acivicin have been reported;[4,5] however, they are all subject to limitations imposed either by length or by stereochemical considerations. A particularly interesting and expeditious route, based upon dipolar cycloadditions of nitrile oxides to vinylglycine derivatives, has been examined by several groups;[5] an attractive feature of this approach is the availability of vinylglycine derivatives in the required enantiomeric form.[6] The main limitation of this approach, however, has been the poor diastereofacial selectivity in the cycloaddition; the wrong C-5 stereoisomer has generally been obtained as the major product, although the levels of diastereoselection are not usually high.[7] We have recently been interested in the synthetic applications of nitrones as an alternative to nitrile oxides, since they allow access to both isoxazolidines and isoxazolines as synthetic intermediates[8] and they can easily carry a chiral auxiliary for asymmetric induction in dipolar cycloadditions.[9] We report herein a short, highly stereoselective total synthesis of acivicin, based upon the principle of double-asymmetric induction[10] in the reaction of chiral nitrones with L-vinylglycine derivatives (Scheme I).

The nitrones **2a–c** used in this work were generated in situ from 5-hydroxypentanal oxime,[11] 2,3:5,6-di-*O*-isopropylidene-D-mannose oxime,[12] and 2,3-*O*-isopropylidene-5-*O*-trityl-D-ribose oxime, respectively, by reaction with paraformaldehyde; the L-vinylglycine derivatives **3a–d** were prepared either directly or by modification of the procedures of Rapoport and of Hanessian.[6] In general, the preparation of the nitrones and the dipolar cycloadditions were carried out in chloroform at reflux as described by Vasella.[12] The N-substituted isoxazolidines isolated from these reactions were converted to N-unsubstituted isoxazolidines by acid hydrolysis (perchloric acid in methanol for cycloadducts of **3a**; formic acid for cycloadducts of **3b–d**) and thence to isoxazolines (**4** and/or **5**) by oxidation with *N*-chlorosuccinimide[12] in methylene chloride. Overall yields for these three steps are indicated in Table I. The diastereoselectivity in the cycloaddition was readily assessed at this stage by ^{1}H NMR spectroscopy; integration of the signals for the proton at C-3 of the isoxazolines gave the product ratios as indicated in Table I. In all cases the slightly broadened singlets observed for **4a–d** and **5a–d** were located near δ 7.20, with the 5*S*-isomer **4** giving the higher field signal. *N*-Carbobenzoxy-L-vinylglycine methyl ester (**3a**) exhibited a modest preference for the 5*R*-isomer **5** when reacted with nitrones **2a** and **2b**, which was reversed with nitrone **2c**. Conversely the methylidene-protected L-vinylglycines **3b–d** exhibited selectivity for the desired 5*S*-stereoisomer **4** with all three nitrones; the selectivity in the reaction of **2c** with **3b–d** was sufficiently great that the minor isomer could not be detected by NMR. It would appear that these last three combinations constitute matched pairs of asymmetric reactants for double-asymmetric induction.[10]

Table I. Diastereofacial Selectivity in Nitrone Cycloadditions

nitrone	alkene	prod ratio **4**:**5**[a]	yield,[b] %
2a	**3a**	2:3	71
2b	**3a**	1:2	72
2c	**3a**	2:1	77
2a	**3b**	2:1	45[c]
2b	**3b**	3:1	60[c]
2c	**3b**	>19:1	74
2c	**3c**	>19:1	74
2c	**3d**	>19:1	80

[a] Measured by ^{1}H NMR. [b] Based upon alkene as the limiting reactant. [c] Yield not optimized.

The final conversion of the isoxazoline **4** to acivicin required two transformations: chlorination at C-3 and deprotection of the amino acid. The chlorination was examined on both the protected amino acids **4a–d** and the corresponding free amino acid and proved initially to cause considerable problems. Eventually a successful and reproducible method was found (excess Cl_2/*tert*-butyl alcohol/25 °C) that allowed conversion of **4d**[13] to the 3-chloroisoxazoline[13] **6d** in 89% yield. The protecting groups were subsequently removed[14] (BCl_3/CH_2Cl_2/25 °C) to give, after purification by ion-exchange chromatography (Dowex 50X8-400, 0.5 N NH_4OH, 56% yield), acivicin[13] (**1**) in an overall yield of 39% based on **3d**. The synthetic material thus obtained was identical in all respects, including optical properties, with the natural product.

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(13) **4d**: ^{1}H NMR ($CDCl_3$) 7.20 (br s, 1 H, H-C3), 5.56 (br, 1 H, CH_2), 5.39 (d, 1 H, J = 4 Hz, CH_2), 5.08 (br, 1 H, H-C5), 4.33 (br, 1 H, H-Cα), 3.80 (s, 3 H), 3.54 (ddd, 1 H, J = 18, 7.5, 2 Hz), 3.24 (ddd, 1 H, J = 18, 11.5, 2 Hz); $[\alpha]^{20}_D$ +269° (c = 0.49, $CHCl_3$). **6d**: ^{1}H NMR ($CDCl_3$) 5.54 (br, 1 H, CH_2), 5.36 (d, 1 H, J = 4 Hz, CH_2), 5.29 (br, 1 H, H-C5), 4.35 (br, 1 H, H-Cα), 3.82 (s, 3 H), 3.69 (dd, 1 H, J = 18, 8 Hz), 3.40 (dd, 1 H, J = 18, 11 Hz); $[\alpha]^{20}_D$ = +277° (c = 0.61, $CHCl_3$). **1**: ^{1}H NMR (D_2O) 5.36 (ddd, 1 H, J = 11, 8, 3 Hz, H-C5), 4.12 (d, 1 H, J = 3 Hz, H-Cα), 3.60 (dd, 1 H, J = 18, 11 Hz, H-C4), 3.52 (dd, 1 H, J = 18, 8 Hz, H-C4); $[\alpha]^{20}_D$ = +139° (c = 0.14, H_2O), $[\alpha]^{20}_{578}$ = +146° (c = 0.14, H_2O).

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