19. Synthesis of 4-Acetylcolchicine

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The synthesis of 4-acetylcolchicine (**1**) by *Swern* dehydrogenation of the corresponding mixture of 4-[(*R*)-1-hydroxyethyl]- and 4-[(*S*)-1-hydroxyethyl]colchicine (**3a** and **3b**, respectively) is described (*cf. Scheme*). The X-ray analysis of **1** (*cf. Fig.*), crystallized from MeOH, showed the presence of MeOH in the crystals.

In the context of our syntheses of 4-alkylcolchicines (*cf.* [1]), we were also interested in the synthesis of 4-acetylcolchicine (= (*S*)-*N*-(4-acetyl-5,6,7,9-tetrahydro-1,2,3,10-tetramethoxy-9-oxobenzo[*a*]heptalen-7-yl)acetamide; **1**) as a possible starting material for other 4-substituted colchicine derivatives. We have already reported that all attempts to prepare **1** from colchicine by well-established electrophilic acylation procedures failed – at least in our hands [1]. Also unsuccessful were synthetic approaches based on the methylation of the 1,3-dithiane derivative of 4-formylcolchicine (**2**; *cf.* [1]). However, more promising was the methylation of **2** with $MeZr(OBu)_3$ according to the procedure developed by *Seebach* and coworkers [2]. The expected diastereoisomers **3a**/**3b** were obtained in a ratio of 9:1 (*Scheme*) [1]. The dehydrogenation of the mixture **3a**/**3b** with freshly prepared MnO_2 [3] in CH_2Cl_2 gave **1** according to TLC analysis in unsatisfactory yields (*cf.* also [4]). Extensive solid-liquid extraction of the MnO_2 did not improve the yield of **1**.

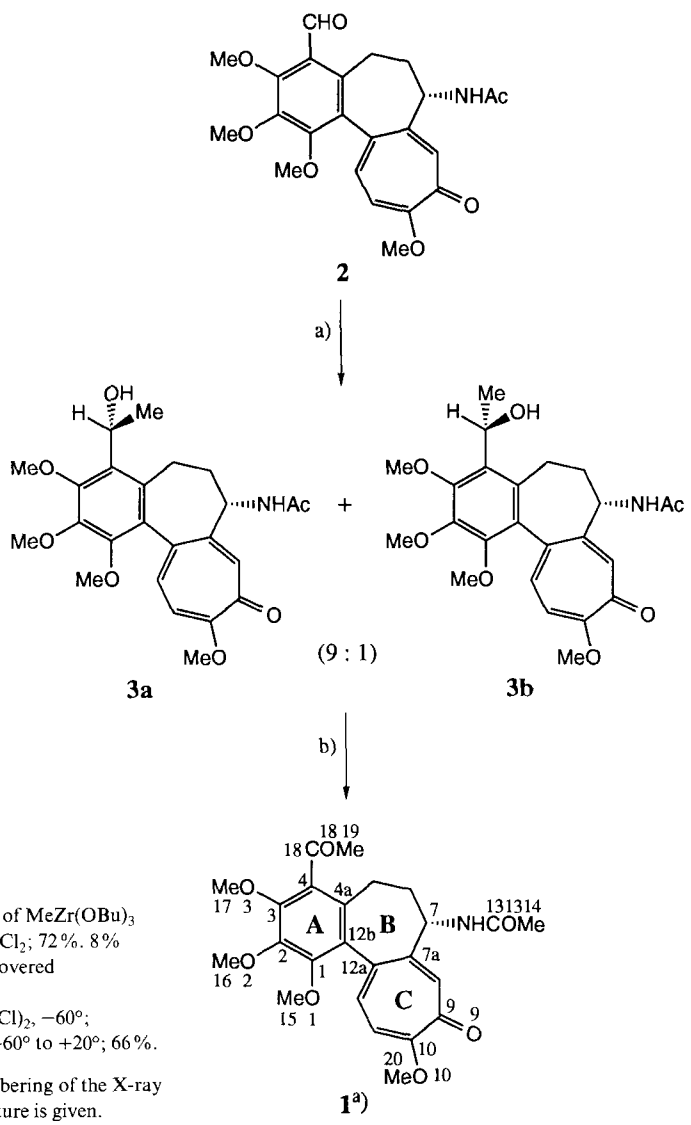
Much better results were obtained, when the mixture **3a**/**3b** was dehydrogenated according to *Swern*'s procedures (*cf.* [5]). 4-Acetylcolchicine (**1**) was obtained as a yellow oil in a yield of 66%. It crystallized after addition of MeOH as colorless crystals (m.p. 164–168°). The m.p. of **1** varied strongly with the solvent from which it was crystallized due to its tendency to form solvate complexes (*cf. Exper. Part*).

Since all attempts to add nucleophiles to the C=O group at C(4) of **1** failed (*cf.* [6]), we performed an X-ray analysis of the crystals of **1** obtained from MeOH. A stereoprojection of the crystal structure is presented in the *Figure*. It clearly shows that the Ac group at C(4) of **1** is in an orthogonal orientation with respect to the plane of ring A. This leads to a nearly complete shielding of the two possible trajectories for a nucleophilic attack at the C=O group by MeO–C(3) on one side and by CH_2(5) of ring B on the other side. However, the crystal structure of **1** itself deserves some more comments.

The compound is enantiomerically pure; however, the absolute configuration has not been determined. The configuration of the enantiomer used in the refinement (7*S*) was assigned to agree with that of naturally occurring (–)-colchicine [8–10]. The packing of

[1]) Part of the Ph.D. thesis of *P.K.*, University of Zurich, 1993.

Scheme



a) 3 mol-equiv. of $MeZr(OBu)_3$ in Et_2O/CH_2Cl_2; 72%. 8% of **2** were recovered (see also [1]).

b) DMSO/$(COCl)_2$, −60°; then Et_3N, −60° to +20°; 66%.

[a]) Atomic numbering of the X-ray crystal structure is given.

the molecules is influenced by an intermolecular H-bond between the amide N-atom and the carbonyl O-atom, O(9), of the seven-membered ring of an adjacent molecule ($H(1)\cdots O(9') = 1.89$ Å, $N\cdots O(9') = 2.790(7)$ Å, $N{-}H(1)\cdots O(9') = 158°$). This H-bond links the molecules into infinite one-dimensional chains which run parallel to the crystal x-axis. The $N\cdots O(9')$ interaction is frequently observed in the solid-state structures of colchicine derivatives. The crystal lattice also contains highly disordered solvent molecules, probably MeOH, because the crystals were obtained from a solution of the

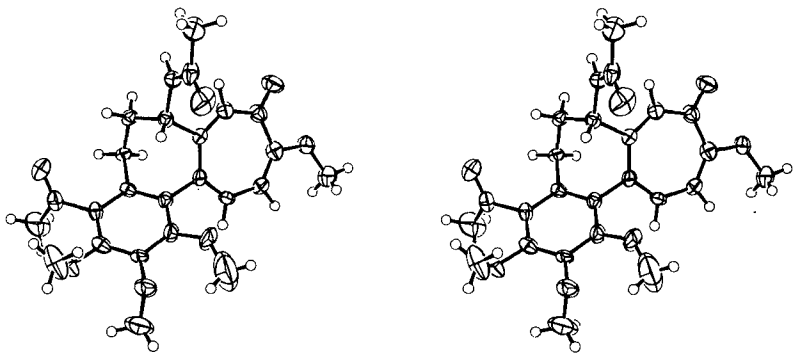


Figure. *Stereoprojection* (ORTEP [7]) *of the molecular structure of* **1**. The solvent molecule has been omitted for clarity.

compound in MeOH. However, the disorder in this region of the structure prevented the exact nature of the solvent atoms from being resolved unequivocally (see *Exper. Part*). The solvent is probably involved in H-bonding with the main substrate molecule, because the carbonyl O-atoms, O(18) and O(13), are within 2.9 Å of the main peaks of electron density associated with the MeOH molecule.

The atomic coordinates from X-ray crystal-structure determinations of 23 colchicine and colchiceine derivatives (excluding structures in which ring B contains a double bond anywhere between C(4a) and C(7a)) are contained in the April 1995 version of the *Cambridge Structural Database* [11]. As noted previously [9] [10], an analysis of the torsion angles within the rings of these compounds shows that they all have very similar conformations, and the conformation of **1** is no exception. Of particular importance is the torsion angle C(4a)–C(12b)–C(12a)–C(7a), which is thought to influence the activity of colchicines during the binding process to tubulin [12]. The mean value of the absolute values of this torsion angle from the 23 structures is 54.6(6)°, and the range of angles is 49–62°. The extremes of this range occur, when the substituent at C(7) is absent, other than N, or the N-atom is charged. The corresponding torsion angle in **1** is 54.9(7)° and, therefore, in accordance with the average value for compounds of this class.

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Experimental Part

General. See [1].

4-Acetylcolchicine (**1**). Oxalyl chloride (0.45 ml, 5.22 mmol) was dissolved in CH_2Cl_2 (10 ml) and cooled in a flame-dried glass apparatus to −60°. A soln. of Me_2SO (0.75 ml, 10.44 mmol) in CH_2Cl_2 (3 ml) was added dropwise under N_2, followed, after 2 min stirring at −60°, by a soln. of a 9:1 mixture (1.93 g, 4.35 mmol) of *4-[(R)-1-hydroxyethyl]-* and *4-[(S)-1-hydroxyethyl]colchicine* (**3a**/**3b**) [1] in CH_2Cl_2 (10 ml). Stirring was continued at −60° for 15 min, and Et_3N (3.0 ml, 75 mmol) was added. The mixture was allowed to warm up to r.t., when H_2O (50 ml) was added. The aq. phase was additionally extracted with CH_2Cl_2. The combined CH_2Cl_2 phases were washed with sat. $NaHCO_3$ soln. and dried ($MgSO_4$). The yellow oil that was left after the evaporation of CH_2Cl_2 was dissolved in MeOH (15 ml) and kept at 0°. Compound **1** crystallized as colorless crystals as a solvate with MeOH (1.36 g, 66%); m.p. 164–168°. Crystals of **1** were also obtained from AcOEt (m.p. 152–153°) or acetone (m.p. 141–143°). However, they also contained solvent molecules.

Spectroscopic Data of the Crystals from MeOH: $[\alpha]_{589}^{20} = -144.3$ ($c = 0.133$, $CHCl_3$). UV (99% EtOH): λ_{max} 342 (4.22), 240 (4.49); λ_{min} 288 (3.67). IR ($CHCl_3$): 3442*m* (NH; free), 3264*m* (br., NH; intermol. bound), 3000*m*, 2965*m*, 2844*m*, 1684*s*, 1616*s*, 1564*s*, 1503*s*, 1461*s*, 1413*s*, 1351*s*, 1258*s*, 1085*s*, 1023*s*. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.84 (*d*, $J = 6.3$, NH); 7.55 (*s*, H–C(8)); 7.28 (*d*, $J = 10.7$, H–C(12)); 6.87 (*d*, $J = 10.9$, H–C(11)); 4.61 (superimp. *dt*, $J = 12.1$, 6.3, H–C(7)); 4.02, 3.98, 3.96, 3.65 (4*s*, 4 MeO); 2.52 (*s*, *Me*CO–C(4)); 2.30 (*sept.*-like *m*, $J = 13.2$, 6.5, H–C(6)); 2.00 (*s*, *Me*CONH); 2.2–1.7 (*m*, H–C(6), CH_2(5)). EI-MS: 443 (100, $M^{+\cdot}$), 400 (16, $[M - MeCO]^+$), 382 (10), 351 (14), 338 (100), 329 (42).

Crystal-Structure Determination of **1**[2]. All measurements were conducted at low-temperature on a *Rigaku AFC5R* diffractometer using graphite-monochromated MoK_α radiation ($\lambda = 0.71069$ Å) and a 12-kW rotating anode generator. The intensities were collected using $\omega/2\theta$ scans. Three standard reflections measured every 150 reflections showed negligible variation in intensity. The intensities were corrected for *Lorentz* and polarization effects, and an empirical absorption corrrection (DIFABS [13]) was applied. The structure was solved by direct methods using SHELXS86 [14] which revealed the positions of all non-H-atoms.

The crystal lattice contains highly disordered solvent molecules in a 1:1 ratio with the molecule **1**. The solvent molecules are probably MeOH, since the crystals were obtained from a soln. of the compound in MeOH. Two orientations of the MeOH molecule were defined, although the choices for the assignment of the electron density peaks to O- and C-atoms may not strictly be correct. It is clear that the solvent occupies many orientations within its cavity, and the model only approximately accounts for the electron density in this region. The non-H-atoms were refined anisotropically, except for those of the solvent molecule, which were refined isotropically. All of the H-atoms of **1** were placed in idealized positions (d(C–H) = 0.95 Å) with fixed isotropic temp. factors calculated as $1.2U_{eq}$ of the parent C- or N-atom. H-Atoms were not included for the solvent molecule. All refinements were carried out on F using full-matrix least-squares procedures. A correction for secondary extinction was applied (coefficient: 1.4×10^{-7}). The data collection and refinement parameters are listed in the *Table*. The crystal quality was sub-standard, which, together with the difficulties in modelling the solvent region, has resulted in slightly higher values than normal for the R factors and the estimated standard deviations of the atomic parameters. The structure also exhibits possible disorder of one of the MeO groups (C(15)); however, it was not possible to successfully refine disordered positions for this group, and, therefore, atom C(15) occupies a mean position with very large thermal parameters and a foreshortened C–O bond.

Table. *Crystallographic Data for Compound* **1**

Crystallized from	MeOH	Z	4
Empirical formula	$C_{24}H_{27}NO_7 \cdot CH_3OH$	D_x [g cm^{-3}]	1.270
Formula weight	473.52	μ(MoK_α) [mm^{-1}]	0.089
Crystal color, habit	colorless, prism	Absorption correction (min; max)	0.77; 1.15
Crystal dimensions [mm]	$0.28 \times 0.35 \times 0.35$	$2\theta_{(max)}$ [°]	60
Temperature [K]	173 (1)	Total reflections measured	4967
Crystal system	orthorhombic	Symmetry independent reflections	4611
Space group	$P2_12_12_1$	Reflections used [$I > 2\sigma(I)$]	2432
Unit cell parameters		Parameters refined	306
Number of centred reflections	22	R	0.0752
2θ range [°]	24–35	wR^a)	0.0709
a [Å]	11.420 (3)	Goodness of fit	2.779
b [Å]	13.036 (3)	Final Δ_{max}/σ	0.02
c [Å]	16.638 (4)	$\Delta\rho$ (max; min) [e Å^{-3}]	0.47; −0.49
V [Å^3]	2477 (1)		

a) Function minimized: $\Sigma w(|F_o| - |F_c|)^2$, where $1/w = [\sigma^2(F_o) + (0.008F_o)^2]$.

Neutral atom-scattering factors for non-H-atoms were taken from [15a] and the scattering factors for H-atoms from [16]. Anomalous dispersion effects were included in F_c [17]; the values for f' and f'' were taken from [15b]. All calculations were performed using the TEXSAN [18] crystallographic software package.

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2) The atomic coordinates, bond lengths, and angles have been deposited with the *Cambridge Crystallographic Data Centre*, 12 Union Road, Cambridge CB2 1EZ, England.

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