Re-functionalisation of α-Substituted Isocolchicides *via* Nucleophilic *Tele*-substitution

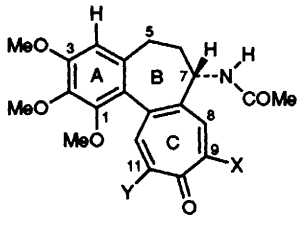
Marino Cavazza[a] and Francesco Pietra[b]

[a] *Dipartimento di Chimica e Chimica Industriale, Università degli Studi di Pisa, 56126 Pisa, Italy*
[b] *Istituto di Chimica, Università degli Studi di Trento, 38050 Povo-Trento, Italy*

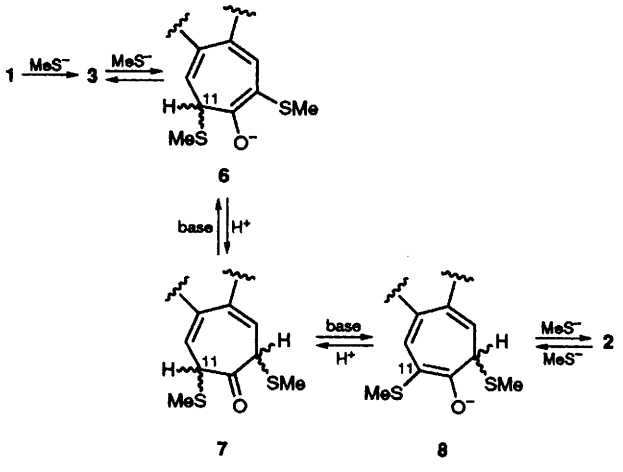
9-Methoxyisocolchicide **1** in excess methanethiolate–methanol, or Me_2SO, slowly undergoes *ipso*-substitution giving 9-methylthioisocolchicide **3**, which then suffers *tele*-substitution giving 11-methylthioisocolchicide **2**; this activation by dicoordinated sulfur is used for amino re-functionalisation of the isocolchicide system.

The main product of the reaction between 9-methoxyisocolchicide **1** and excess sodium methanethiolate in methanol–water 83:17[1] was 11-methylthioisocolchicide **2**.[2] However, the interpretation of this process as occurring *via tele*-substitution by MeS^- on **1**[2] contrasts with current views on the mechanism of nucleophilic substitution on troponoids, where the α-methoxy group deactivates the cycloheptatrienone ring, allowing only *ipso*-substitution.[3] Here, we show that this interpretation[2] cannot be maintained and that the process can be used for novel re-functionalisation of isocolchicinoids.

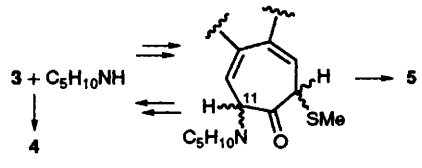
In a mixture with NaSMe in MeOH–H_2O 83:17, as originally described[1,2] but on a 50-fold smaller scale, **1** disappeared in three days to give predominantly **3**.† The latter (0.04 mol dm^{-3}) and 15-fold molar excess NaSMe led, after three days at room temp, to a **2**:**3** ratio of 0.09 (solvent MeOH) or 0.5 (solvent Me_2SO). Clearly, the methoxy substituent only allows *ipso*-substitution, giving **3**, while the methylthio substituent induces *tele*-substitution by which **3** gives **2** in competition with the back reaction (Scheme 1). In fact, when pure **2** was mixed with a 15-fold molar excess of NaSMe in MeOH, **3**:**2** in a 0.4 ratio was obtained after three days at room temp.



1 X = OMe, Y = H
2 X = H, Y = SMe
3 X = SMe, Y = H
4 X = NC_5H_{10}, Y = H
5 X = H, Y = NC_5H_{10}



Scheme 1 Proposed mechanism for *tele*-substitution on either 9-methylthioisocolchicide 3 or 11-methylthioisocolchicide **2** by sodium methanethiolate.



Scheme 2 Competing *ipso*- (to **4**) and *tele*-substitution (to **5**) with 9-methylisocolchicide **2** and piperidine.

The electron acceptance by dicoordinated sulfur[4] can be exploited in novel re-functionalisation of the isocolchicide skeleton, *e.g.* amino re-functionalisation.

Heating a solution of **3**‡ (0.04 mol dm^{-3}) in 2:1 Me_2SO–piperidine at 49 °C for 40 h led to 11-piperidinoisocolchicide **5** (19%) and 9-piperidinoisocolchicide **4** (57%).§ Here, the C-11 is activated by the C-2 SMe substituent, (Scheme 2).¶‖ In agreement, reaction of **1** with piperidine under the above conditions led rapidly to **4** in quantitative yields, no trace of **5** being detectable by HPLC.

We thank Mr A. Sterni for skilled technical aid with mass spectra and MURST (Progetti 40% and 60%) and CNR, Roma, for financial support.

Received, 14th December 1993; Com. 3/07372F

Footnotes

† Previously reported[1,2] good yields of **2** resulted from spontaneous crystallization of this compound[1,2]

‡ Compound **3** can be conveniently obtained in quantitative yields by the reaction of 9-tosyloxy- or 9-mesyloxy-isocolchicide[5] with 1 equiv. of methanethiolate in Me_2SO

§ Yields are given on reacted substrate. The structures are fully supported by NMR and HRMS data. **4**: mp 135–140 °C; λ_{max}/log ε (EtOH) 263/4.20, 373/4.14, 400sh/4.1. **5**: mp 108–110 °C; α_{max}/log ε (EtOH) 263/4.30, 324/4.40, 420/4.10.

¶ Owing to the deactivating properties of the amino substituent,[3,6] all **4** must have arisen from *ipso*-substitution.

‖ This is a general amino re-functionalisation and it is likely it could be extended to other nucleophiles. In contrast, *tele*-substitution observed on 7-deacetyl-11-tosyloxyisocolchicide by ammonia[7] is unlikely to represent a general case of amino re-functionalisation. With a good leaving group like tosyloxy, ammonia[7] was lucky to be *tele*-substituted;[6] the stronger nucleophile piperidine only gives *ipso*-substitution under such conditions, in agreement with the theory (ref. 6 and above).

References

1 L. Velluz and G. Muller, *Bull. Soc. Chim. Fr.*, 1955, 198.
2 B. Danieli, G. Lesma, G. Palmisano and R. Riva, *Helv. Chim. Acta*, 1985, **68**, 2173.
3 F. Pietra, *Acc. Chem. Res.*, 1979, **12**, 132.
4 G. Biggi and F. Pietra, *J. Chem. Soc., Chem. Commun.*, 1973, 229; C. A. Veracini and F. Pietra, *J. Chem. Soc., Chem. Commun.*, 1974, 623; E. Farina, C. A. Veracini and F. Pietra, *J. Chem. Soc. Chem. Commun.*, 1974, 672; R. Cabrino, E. Farina, F. Del Cima and F. Pietra, *J. Chem. Soc., Perkin Trans. 1*, 1976, 2214; M. Cavazza, C. A. Veracini, G. Morganti, *Tetrahedron Lett.*, 1978,

2593; M. Cavazza, G. Morganti, A. Guerriero and F. Pietra, *Tetrahedron Lett.*, 1980, 3703.
5 M. Cavazza, C. A. Veracini and F. Pietra, *J. Chem. Soc., Perkin Trans. 2*, 1992, 2201.
6 G. Biggi, F. Del Cima and F. Pietra, *J. Am. Chem. Soc.*, 1973, **95**, 7101.
7 J. Schreiber, W. Leimgruber, M. Pesaro, P. Schudel and A. Eschenmoser, *Angew. Chem.*, 1959, **71**, 637.