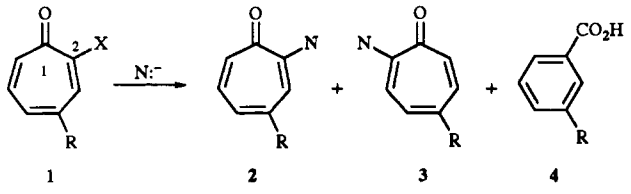
ipso- vs. tele-Nucleophilic substitution by piperidine on isocolchicides and colchicides bearing an α-leaving group

Marino Cavazza[a] **and Francesco Pietra**[b]
[a] *Dipartimento di Chimica e Chimica Industriale, Universita di Pisa, 56126 Pisa, Italy*
[b] *Istituto di Chimica, Università di Trento, 38050 Povo-Trento, Italy*

Product studies of the reactions of piperidine with colchicides carrying a C-10 nucleofugic group show that only *ipso* substitution occurs. For isocolchicides carrying an X nucleofugic group at C-9, similar behaviour was observed for X = F, OTs or OMe, while for X = SMe, SOMe or Cl *tele* substitution (at C-11) competes with *ipso* substitution. These results together with the observation that the reaction rates for the two series are similar, may be useful in guiding the refunctionalization of similar compounds.

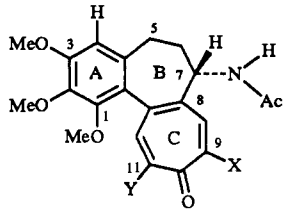
The behaviour of simple troponoids towards nucleophiles, *inter alia* the competition between *ipso*- and *tele*-substitution[1] and ring contraction to benzenoids[2] (Scheme 1), has been



Scheme 1

extensively studied.[3] Ring contraction (Scheme 1, **1**→**4**), typically occurs with hard anionic nucleophiles, especially OH^-, while *tele*-substitution (Scheme 1, **1**→**3**) is typical of (a) protic nucleophiles in non-polar, aprotic media, owing to proton coordination with, and transfer to, C(1)–O^-, which makes the nucleophile a poor nucleofuge, or (b) troponoids that carry typically poor α-nucleofuges, which are changed to good nucleofuges by coordination of C(1)–O^- to an electrophile, such as Li^+ in a non-polar solvent.[4] *tele*-Substitution is also favoured by electron-attracting C-2 substituents which are also good nucleofuges, such as Cl and $^+NR_3$. Conversely, a poor nucleofuge that is also a deactivating group, like OMe, can only undergo *ipso*-replacement, unless, with anionic nucleophiles, attack is forced at Me, with tropolonate release.[5]

We have recently extended these studies to colchicinoids, observing covalent adducts with alkoxides or thiolates,†[6] and reexamined Velluz's reaction of **5** with MeSH to give **6**.[7] The



5 X = OMe, Y = H
6 X = H, Y = SMe

Scheme 2

† Unlike the results from previous experiments,[6] this time we isolated, after deuterium exchange and diazomethane methylation, colchicine deuteriated at the amide chain.

Table 1 Preparative product-yield(s) and rate coefficient for product(s) formation in the reactions of piperidine with various isocolchicides carrying a C-9 nucleofugic group in DMSO (at 18 °C, unless otherwise stated)

	Product (%)[a]		
Compound	**8** *ipso* substitution	**9** *tele* substitution	$10^4 \times k_{obs}$[b] / $mol^{-1}\ dm^3\ s^{-1}$
12 (X = F)	100	0	114 000
13 (X = OTs)	100	0	360
7 (X = Cl)	90	10	130
10 (X = SOMe)	79	21	2
5 (X = OMe)	100	0	—
11 (X = SMe)	75	25	1.3[c]

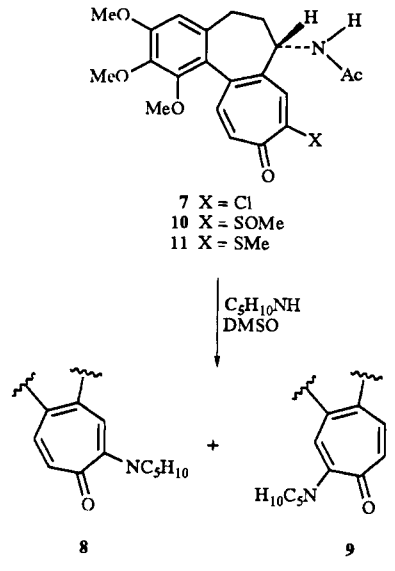
[a] At complete reaction under preparative conditions (see Experimental Section and ref. 10). [b] It represents the overall rate coefficient for formation of product(s) under pseudo-first order conditions (substrate 10^{-4}-10^{-5} mol dm^{-3}; piperidine 6.7×10^{-2}, except for **12**, where piperidine 6.7×10^{-4} mol dm^{-3}) divided by the piperidine concentration. [c] At 53 °C.

latter must arise from initial *ipso* replacement of the methoxy group, followed by *tele* substitution at C-11 (ruling out the proposed[9] *tele*-substitution on **5**[9]) according to our general rules,[3] and electron acceptance by dicoordinated sulfur at C-9 in simple troponoids.[10] On this basis, 9-SR substituted isocolchicinoids could be refunctionalized at C-11 by amines.[8] Moreover, we devised an easy route, by reaction of the BF_3 adduct of colchiceine with an amine, to 10-aminocolchicides.[11]

Since colchicinoids are attracting much interest as potential agents for the control of plant diseases and pests, other than as biolaboratory tools, we deemed it worthwhile to examine colchicinoids bearing a wider variety of leaving groups and to carry out semiquantitative kinetics with the aim of optimizing the conditions for synthesis.

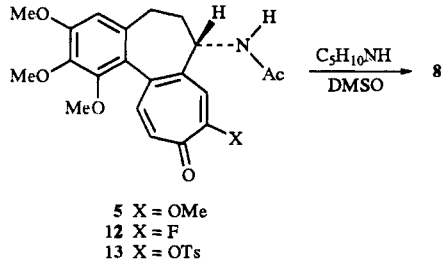
Results and discussion

After having observed a 75:25 ratio for *ipso vs. tele* substitution of 9-methylsulfanylisocolchicide **11** by piperidine (Table 1, Scheme 3),[8] we have now examined the competition of these two processes in a series of other 9-substituted isocolchicides. The results in Table 1 show that the 9-methylsulfinyl substituent **10** gives nearly as much *tele*-substitution as the 9-methylsulfanyl substituent. The 9-chloro substituent **7** proved also to be *tele* directing, although less efficiently so (Scheme 3). In contrast, 9-fluoro- **12**, 9-tosyloxy- **13** and 9-methoxy-substituted **5**



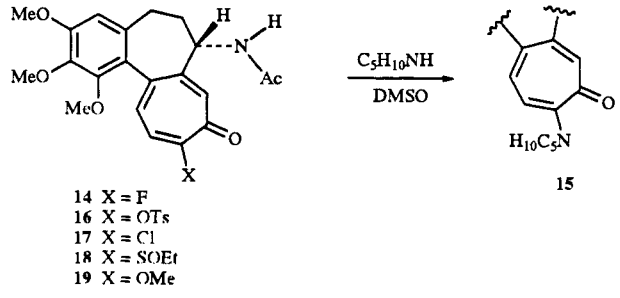
Scheme 3

isocolchicides only showed *ipso* substitution (Table 1, Scheme 4).



Scheme 4

10-Substituted colchicides proved to be a simpler series, in which only *ipso* substitution by piperidine occurred irrespective of the nature of the leaving group (Scheme 5).



Scheme 5

The structures of new compounds **7**,‡ **10**, **12**, **14**, **17** and **18** rest on both NMR and MS data,§ as well as on transformation products.

‡ A compound assigned as **7** has appeared in the literature, though not characterized (R. M. Chabin, F. Feliciano and S. B. Hastie, *Biochemistry*, 1990, **29**, 1869).

§ Because of the great tendency of the troponoid ring to retain solvents of crystallization, HR-MS data provide better confirmatory evidence of product identity than elemental analysis. Homogeneity of the compounds is proven by quite clean NMR—and fully assigned—spectra, in accordance with single TLC spots in any reported case.

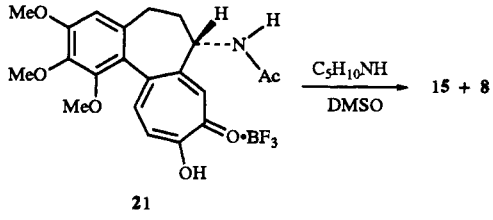
Kinetics for the above processes were carried out under conditions unavoidably far different from the preparative experiments. While the latter were carried out at high substrate concentration in piperidine–Me_2SO (1:3), the former were followed spectrophotometrically under conditions of very dilute substrate concentration and with an excess of amine. We also omitted partitioning the rate data for the competitive processes of *ipso vs. tele* substitution, the kinetics being carried out at a single temperature (Table 1). More detailed kinetic data were obtained for colchicinoids, where no problems of partitioning the rate data arose (Table 2).

Kinetics proved to be of second order overall, first order in both the substrate and the amine. The kinetics for both isocolchicides and colchicides carrying a nucleofugic group at C-9 (Table 1) or C-10 (Table 2) span a factor *ca.* 10^6 from the slowest (9-methylsulfanyl) to the fastest (9-F) substrate. Also the trend of rates for the intermediately mobile leaving groups proved to be very similar in the two series. This may be interpreted in terms of lack of conjugation between the cycloheptatrienone and the arene moieties.

Comparison of colchicinoids and isocolchicinoids on the one hand with troponoids on the other, is not straightforward, however. From the limited data available, it seems that relative rate data for troponoids are more compressed in benzene[12] than in DMSO as solvents.[13] Present rate data for colchicinoids and isocolchicinoids span a much larger interval, at least when the least replaceable are compared with the most replaceable leaving groups (OMe *vs.* F).

Unlike reactions of troponoids in benzene,[14] no isokinetic relationship is observed with colchicinoids (Table 2).

Schemes 3–6 and the kinetic data in Tables 1–2 are for guidance in the planning of syntheses: they show that (a) C-10 aminocolchicides (**15**-type) are best obtained from the BF_3 adduct of colchiceine **21**. The higher reactivity and



Scheme 6

regioselectivity of 10-fluorocolchicide **14** does not justify the effort and cost needed for its preparation. The speed of the reaction of **21** is sufficient for preparative chemistry; (b) for 9-aminocolchicides (**8**-type) there is a choice between obtaining them either as by-products of the reaction of the amine with the BF_3 adduct of colchiceine **21**[11] or from the reaction of **13**. The former process is easier to carry out, though of low yield.

Lack of *tele* substitution in colchicinoids probably results from steric compression in the tetrahedral intermediate of amine attack at C-8.

Experimental

General

All evaporations were carried out under reduced pressure and yields are based on reacted substrate. Me_2SO was freshly distilled in flamed glassware from CaH_2 and stored on 4 Å molecular sieves in Schlenk tubes under N_2. TLC was performed on Merck Kieselgel $60PF_{254}$ and reversed phase HPLC on Perisorb RP18 4.4 × 250 mm with MeCN–H_2O (1:1; 1 cm^3 min^{-1}). UV spectra were taken with a Perkin-Elmer Hitachi 200 spectrophotometer equipped with a thermostatted

Table 2 Overall rate coefficient for formation of **15** in the reactions of piperidine with various colchicides carrying a C-10 nucleofugic group in DMSO

Compound	$10^4 \times k_{obs}$ [a] / mol^{-1} dm^3 s^{-1}			$\Delta H^{\ddagger}$	$\Delta S^{\ddagger}$
	17.2 °C	29.0 °C	38.0 °C	kcal mol^{-1}	e.u.
14 (X = F)	143 300	191 000	246 300	5.5	−38.3
16 (X = OTs)	910	1 070	1 640	4.7	−51.5
17 (X = Cl)	142	233	319	7.7	−44.4
18 (X = SOEt)	2.8	3.7	5.5	6.5	−57.0
19 (X = OMe)	0.33	—	1.17	9.4	−50.5
20 (X = SEt) [b]	—	—	—	—	—

[a] It represents the overall rate coefficient for formation of product(s) under pseudo-first order conditions (substrate 10^{-4}-10^{-5} mol dm^{-3}; piperidine 6.7×10^{-2}, except for **14**, where piperidine 6.7×10^{-4} mol dm^{-3}), divided by the piperidine concentration. [b] $10^4 \times k_{obs} = 0.46$ mol^{-1} dm^3 s^{-1} at 53 °C.

cell compartment for kinetic measurements. NMR spectra were taken with a Varian Gemini BB200 (199.975 MHz on ^{1}H, 50.289 MHz on ^{13}C, 188.143 on ^{19}F, 64.167 on ^{11}B). δ_F Values are with respect to external BF_3·OEt_2 ($\delta = 0$) and J values are recorded in Hz. Mass spectra (EI) were taken with a Kratos MS80 spectrometer with a home-built computerized acquisition system.

Synthesis of 9-fluoroisocolchicide 12 and 10-fluorocolchicide 14

A mixture of colchiceine (0.20 g, 0.52 mmol) and SF_4 (1.8 g) in a Hastelloy bomb was heated for 8 h at 60 °C and then left at room temperature (RT) for 2 days. The yellow reaction mixture was then subjected to TLC with acetone–$CHCl_3$, (1 : 1), two yellow bands at R_F 0.56 (**12**, 0.020 g, 11% yield) and 0.48 (**14**, 0.82 g, 43%) being collected besides unchanged colchiceine (R_F 0.19, 0.013 g).

Data for compound **12**: λ_{max}(MeOH)/nm 230 and 335 (log ε/dm^3 mol^{-1} cm^{-1} 4.1 and 3.9); δ_C($CDCl_3$) 177.50, 177.20, 170.59, 167.45, 162.25, 154.299, 150.96, 144.32, 144.13, 142.73, 139.81, 136.93, 136.67, 135.11, 125.31, 118.27, 117.64, 107.68, 107.51, 61.77, 61.46, 59.19, 52.32, 38.32, 38.15, 29.93, 29.73 and 22.92; δ_H(CD_3COCD_3) 1.80 (3 H, s, Ac), 2.3–2.1 (2 H, series of m, 6-H), 2.50 (2 H, m, 5-H), 3.77, 3.72, 3.54 (3 × 3 H, s, for the 3 MeO), 4.32 (1 H, td, J 12.7, 6.3, 7-H), 6.69 (1 H, s, 4-H), 6.98 (1 H, dd, $J_{11,12}$ 12.97, $J_{11,F}$ 9.35, 11-H), 7.31 (1 H, d, $J_{12,11}$ 12.97, 12-H), 7.43 (1 H, d, $J_{F,8}$ 22.75, 8-H) and 7.68 (1 H, d, J 6.3, NH); δ_F($CDCl_3$) −96.80 (dd, J 22.75, 9.35); m/z (%) 387 (M$^{\cdot+}$, 100) [Found: m/z (HRMS) 387.148 10. Calc. for $C_{21}H_{22}FNO_5$ 387.148 20].

Data for 14

λ_{max}(MeOH)/nm 232 and 340 (log ε/dm^3 mol^{-1} cm^{-1} 4.2 and 3.9); δ_C($CDCl_3$) 177.55, 177.18, 170.17, 167.28, 162.0, 154.12, 153.98, 151.12, 142.56, 142.41, 141.70, 134.34, 134.14, 125.01, 120.43, 119.87, 107.41, 61.68, 61.40, 56.16, 56.12, 52.86, 36.13, 29.80 and 22.74; δ_H(CD_3COCD_3) 1.80 (3 H, s, Ac), 2.36–2.10 (2 H, series of m, 6-H), 2.52 (2 H, m, 5-H), 3.77, 3.73, 3.51 (3 × 3 H, s, for the 3 MeO), 4.38 (1 H, td, J 12.7, 6.6, 7-H), 6.66 (1 H, s, 4-H) 7.02 (1 H, dd, $J_{12,11}$ 10.44, $J_{12,F}$ 3.80, 12-H), 7.29 (1 H, d, $J_{8,F}$ 9.0, 8-H), 7.32 (1 H, dd, $J_{11,12}$ 10.44, $J_{11,F}$ 19.4, 11-H) and 7.74 (1 H, d, J 6.6, NH); m/z (%) 387 (M$^{\cdot+}$, 60) [m/z (HRMS) 387.148 02. Calc. for $C_{21}H_{22}FNO_5$ 387.1482].

Synthesis of 9-chloroisocolchicide 7 and 10-chlorocolchicide 17

To colchiceine (0.083 g, 0.21 mmol) in dry benzene (1 cm^3) was added $SOCl_2$ (0.050 cm^3) and the suspension was heated at reflux for 40 min. The mixture was then evaporated and the dark gummy residue was subjected to TLC with acetone–$CHCl_3$ (1 : 1) two yellow bands at R_f 0.66 (**7**, 0.007 g, 8.3%) and 0.50 (**17**, 0.015 g, 18%) being collected.

Data for **7**: λ_{max}(MeOH)/nm 340 and 245 (log ε/dm^3 mol^{-1} cm^{-1} 3.9 and 4.5); δ_C($CDCl_3$) 179.33, 170.14, 142.78, 141.19, 141.06, 135.26, 135.02, 132.89, 107.69, 61.81, 61.49, 56.19, 52.25, 38.52, 29.91, 29.75, 29.32 and 23.06; δ_H($CDCl_3$) 2.07 (3 H, s, Ac), 2.35–2.15 (2 H, series of m, 6-H), 2.55 (2 H, m, 5-H), 3.70, 3.91, 3.94 (3 × 3 H, s, for the 3 MeO), 4.56 (1 H, td, J 12.6, 6.2, 7-H), 6.58 (1 H, s, 4-H), 7.43 and 7.16 [2 H, AB system, J(AB) 12.8, 11-H and 12-H], 7.99 (1 H, s, 8-H); m/z (%) 403 (M$^{\cdot+}$, 38) [Found m/z (HRMS) 403.116 95. Calc. for $C_{21}H_{22}ClNO_5$ 403.118 65].

Data of **17**: λ_{max}(MeOH)/nm 345 and 240 (log ε/dm^3 mol^{-1} cm^{-1} 3.9 and 4.3); δ_C($CDCl_3$) 180.0, 169.95, 151.79, 143.72, 135.64, 134.18, 133.75, 132.57, 107.47, 61.79, 61.44, 56.16, 52.37, 36.28, 29.85, 29.74, 22.96; δ_H($CDCl_3$) 1.99 (3 H, s, Ac), 2.35–2.15 (2 H, series of m, 6-H), 2.55 (2 H, m, 5-H), 3.93, 3.90 and 3.67 (3 × 3 H, s, for the 3 MeO), 4.62 (1 H, td, J 12.6, 6.2, 7-H), 6.53 (1 H, s, 4-H), 7.83 and 7.16 [2 H, AB system, J(AB) 10.3, 11-H and 12-H], 7.32 (1 H, d, J 6.2, NH), 7.55 (1 H, s, 8-H); m/z (%) 403 (M$^{\cdot+}$, 23) [Found: m/z (HRMS) 403.117 27. Calc. for $C_{21}H_{22}ClNO_5$ 403.118 65].

Synthesis of 9-piperidinoisocolchicide 8 and 11-piperidinoisocolchicide 9

This reaction was carried out from piperidine and **11** as already described in preliminary form;[11] the reaction mixture was subjected to reversed-phase HPLC, to give **8** and **9** (t_R 4.4 and 5.4 min, respectively).

Data for **8**: λ_{max}(MeOH)/nm 264 and 373 (log ε/dm^3 mol^{-1} cm^{-1} 4.20, 4.10); δ_C($CDCl_3$) 181.68, 169.17, 157.89, 152.90, 144.11, 138.36, 134.88, 132.56, 132.07, 107.33, 61.45, 61.36, 56.16, 52.96, 50.56, 38.54, 30.04, 26.10, 24.69 and 22.99; δ_H($CDCl_3$) 1.65 and 3.30 (6 H and 4 H, m, piperidine protons), 1.97 (3 H, s, Ac), 1.90–2.5 (2 H, series of m, 6-H), 2.55 (2 H, m, 5-H), 3.65, 3.62 and 3.58 (3 × 3 H, s, for the 3 MeO), 4.52 (1 H, m, 7-H), 6.38 (1 H, br s, NH), 6.48 (1 H, s, 4-H), 7.17 and 6.86 [2 H, AB system, J(AB) 12.4, 11-H and 12-H] and 6.86 (1 H, s, 8-H); m/z (%) 452 (M$^{\cdot+}$, 17) [Found: m/z (HRMS) 452.231 61. Calc. for $C_{26}H_{32}N_2O_5$: 452.231 12].

Data of **9**: λ_{max}(MeOH)/nm 263, 324 and 370 (log ε/dm^3 mol^{-1} cm^{-1} 3.9, 4.2, 3.7); δ_C($CDCl_3$) 181.67, 169.90, 157.88, 152.90, 139.97, 136.50, 134.93, 134.51, 130.94, 125.04, 107.41, 61.74, 61.58, 56.14, 51.41, 50.54, 33.60, 30.21, 26.11, 24.70, 23.18; δ_H($CDCl_3$) 1.60, 3.12 and 3.30 (6 H, 2 H and 2 H, m, piperidine protons), 1.97 (3 H, s, Ac), 1.90–2.5 (2 H, series of m, 6-H), 2.60 (2 H, m, 5-H), 3.88, 3.85 and 3.58 (3 × 3 H, s, for the 3 MeO), 6.22 (1 H, br s, NH), 6.49 (1 H, s, 4-H), 7.15 and 6.98 [2 H, AB system, J(AB) 12.7, 8-H and 9-H], 6.91 (1 H, s, 12-H); m/z (%) 452 (M$^{\cdot+}$, 80) [Found: m/z (HRMS) 452.230 94. Calc. for $C_{26}H_{32}N_2O_5$ 452.231 12].

Synthesis of 9-methylsulfinylisocolchicide 10

To a solution of 9-methylsulfanylisocolchicide (0.10 g, 0.24 mmol) in CH_2Cl_2 (2 cm^3) at 0 °C was added dropwise a solution of MCPBA (0.038 g) in CH_2Cl_2 (2 cm^3). After 3 h the mixture was washed with dilute aqueous sodium hydrogen carbonate, dried (Na_2SO_4) and evaporated. The residue was subjected to TLC with acetone–$CHCl_3$ (2:3) with collection of the yellow band at R_f 0.31 containing the diastereoisomeric mixture **10** (0.057 g, 55%).

Data for **10** as 1:1 mixture of two diastereoisomers: λ_{max}(MeOH)/nm 230, 320 and 375 (log ε/dm^3 mol^{-1} cm^{-1} 4.6, 4.2, 3.8); δ_C($CDCl_3$) 182.47, 182.35, 170.59, 170.52, 155.50, 155.13, 154.58, 151.20, 145.32, 145.07, 143.29, 143.19, 142.97, 141.67, 137.36, 137.30, 137.19, 135.43, 145.36, 131.42, 126.77, 125.43, 125.30, 107.77, 107.67, 61.98, 61.91, 61.79, 61.51, 61.44, 61.26, 56.25, 56.18, 56.11, 52.45, 41.04, 39.94, 39.89, 38.37, 30.07, 29.71, 22.75 and 22.72; δ_H($CDCl_3$) 2.02 (3 H, s, Ac), 2.4–2.1 (2 H, series of m, 6-H), 2.55 (2 H, m, 5-H), 3.92, 3.90, 3.71 (3 × 3 H, s, for the 3 MeO), 4.60 (1 H, dd, *J* 6.14, 11.72, 7-H), 6.58 (1 H, s, 4-H), 7.52 and 6.99 [2 H, AB system, *J*(AB) 12.7, 11-H and 12-H], 7.80 (1 H, d, *J* 6.14, NH) and 8.17 (1 H, s, 8-H); *m/z* (%) 431 ($M^{\cdot+}$, 90) [Found: *m/z* (HRMS) 431.139 20. Calc. for $C_{22}H_{25}NO_6S$ 431.140 26].

Synthesis of 9-methylsulfanylisocolchicide 11

This compound was prepared in 65% yield following a described procedure;[7] R_f (TLC) 0.51 (acetone–$CHCl_3$ 2:3).

Data for **11**: λ_{max}(MeOH)/nm 261, 290, 363, 381 (log ε/dm^3 mol^{-1} cm^{-1} 4.3, 4.10, 4.30 and 4.29); δ_C as previously reported;[9] δ_H($CDCl_3$) (reassignment with respect to lit.[9]) 2.07 (3 H, s, Ac), 2.5–1.9 (2 H, series of m, 6-H), 2.6 (2 H, m, 5-H), 2.42 (3 H, s, Me), 3.93, 3.90 and 3.67 (3 × 3 H, s, for the 3 MeO), 4.62 (1 H, td, *J* 12.6, 6.6, 7-H), 6.57 (1 H, s, 4-H), 7.44 and 6.98 [2 H, AB system, *J*(AB) 12.6, 11-H and 12-H], 7.35 (1 H, s, 8-H) and 8.20 (1 H, d, *J* 6.6, NH).

Synthesis of the colchiceine–BF_3 adduct 21

The process was initially carried out as described above for the synthesis of the fluoro compounds **12** and **14**, except for the addition of finely grounded Pyrex glass (2 g) to colchiceine (0.2 g). The yellow reaction mixture was subjected to TLC with acetone–$CHCl_3$ (1:1), with collection, besides the yellow bands for **12** (0.0090 g, 45% yield) and **14** (0.030 g, 15%), of a yellow band at R_F 0.73 for **21** (0.020 g). Once the nature of **21** was understood as a BF_3 adduct of colchiceine, the synthesis of **21** was carried out by modifying the method used for the tropolone•BF_3 adduct.[15] Thus, to a solution of colchiceine (0.17 g, 0.3 mmol) in MeOH (0.5 cm^3) was added BF_3•OEt_2 in excess (0.05 cm^3). The resulting yellow solution was evaporated to dryness and the oily residue, though failing to crystallize, was purified by TLC with $CHCl_3$–acetone (3:2), obtaining, from the R_F 0.67 band, **21** (0.1 g, 0.22 mol).

Data for compound **21** (not reported in ref. 11): yellow crystals that decompose when heated; λ_{max}(MeOH)/nm 370 (log ε/dm^3 mol^{-1} cm^{-1} 4.4); δ_C($CDCl_3$) 187.18, 184.72, 170.35, 160.36, 148.04, 137.60, 134.55, 123.15, 121.80, 107.72, 107.65, 56.18, 53.83, 37.67, 29.76, 29.60, 29.34, 22.81, 13.84; δ_H(CD_3COCD_3) 1.98 (3 H, s, Ac), 2.50–2.10 (2 H, series of m, 6-H), 2.65 (2 H, m, 5-H), 3.92, 3.89 and 3.60 (3 × 3 H, s, for the 3 MeO), 4.65 (1 H, m, 7-H), 6.86 (1 H, s, 4-H), 8.31 and 7.92 [2 H, AB system, *J*(AB) 11.2, 11-H and 12-H], 8.12 (1 H, s, 8-H); *m/z* (%) 433 ($[M - HF]^+$, 100), 405 ($[M - HF - CO]^+$, 28) [Found: *m/z* (HREI-MS) 432.152 17 ± 0.0002. Calc. for $C_{21}H_{22}{}^{10}BF_2NO_6$ 432.154 46]. The EI-MS behaviour of the tropolone•BF_3 adduct, reexamined here, proved to be similar. Actually the work reported here started from the serendipitous observation that attempts to prepare the fluorocolchicines **12** and **14** from colchiceine and SF_4 in a Hastelloy bomb,[12] wherein a Pyrex ampoule had been inadvertently left, led to raw material that resisted full characterization but showed the reactivity described here for the adduct **21**.

Synthesis of 10-ethylsulfinylcolchicide 18

The process from 10-ethylthiocolchicide **20** (0.090 g, 0.21 mmol) was carried out in analogy with the preparation of **10** above.[7] TLC with acetone–$CHCl_3$ (2:3) gave, from the R_f 0.41 yellow band, **18** (0.057 g, 61%).

Data for **18** (1:1 mixture of two diastereoisomers): λ_{max}(MeOH)/nm 233, 310, 388 (log ε/dm^3 mol^{-1} cm^{-1} 4.3, 4.0, 4.1); δ_C($CDCl_3$) 182.65, 182.59, 169.78, 169.72, 154.37, 154.20, 153.77, 153.50, 153.18, 151.45, 151.31, 145.80, 135.04, 134.74, 134.58, 134.12, 133.99, 126.76, 125.03, 107.41, 107.19, 61.72, 61.40, 56.18, 56.10, 52.52, 46.31, 45.32, 36.20, 29.75 and 22.99; δ_H(CD_3COCD_3) 1.15 (2 × 3 H, t, *J* 7.2, CH_3CH_2SO), 1.90 (6 H, s, Ac), 2.30–2.0 (4 H, m, 6-H), 2.45 (4 H, m, 5-H), 2.70 and 3.20 (4 H, m, CH_3CH_2SO), 3.92, 3.89 and 3.69 (6 × 3 H, s, MeO), 4.50 (2 H, m, 7-H), 6.79 (2 H, s, 4-H), 7.19 (2 H, s, 8-H), 7.68 and 7.42 [2 H, AB system, *J*(AB) 9.60, 11-H and 12-H, for one diastereoisomer], 7.73 and 7.47 [2 H, AB system, *J*(AB) 9.60, 11-H and 12-H for the other diastereoisomer] and 7.80 (2 H, d, *J* 6.6, NH); *m/z* (%) 416 ($M^{\cdot+}$ − Et, 1.4), 368 ($M^{\cdot+}$ − EtSO, 13) and 357 (100) (Found: C, 62.0; H, 6.0; S, 7.2. $C_{23}H_{27}NO_6S$ requires C, 62.0; H, 6.11; S, 7.18%).

Synthesis of 10-piperidinocolchicide 15

To a solution of compound **16** (0.021 g, 0.038 mmol) in dry DMSO (1 cm^3) was added neat piperidine, 0.2 cm^3. After 10 min, the mixture was added to water which was then extracted with $CHCl_3$; work-up gave practically pure **15** in quantitative yield.

Data for **15**: λ_{max}(MeOH)/nm 260 and 376 (log ε/dm^3 mol^{-1} cm^{-1} 4.2 and 4.1.); δ_C($CDCl_3$) 181.37, 169.88, 158.83, 153.02, 151.50, 149.55, 136.34, 134.53, 133.10, 128.38, 129.10, 117.62, 107.31, 51.47, 56.13, 51.85, 50.20, 37.10, 30.18, 26.02, 24.69 and 23.09; δ_H($CDCl_3$) 1.70, 3.38 and 3.48 (6 H, 2 H and 2 H, m, piperidine H), 1.99 (3 H, s, Ac), 1.90–2.50 (2 H, series of m, 6-H), 2.55 (2 H, m, 5-H), 3.91, 3.86 and 3.63 (3 × 3 H, s, for the 3 MeO), 4.60 (1 H, m, 7-H), 6.49 (1 H, s, 4-H), 7.21 and 6.76 [2 H, AB system, *J*(AB) 11.1, 11-H and 12-H] and 7.26 (1 H, s, 8-H); *m/z* (%) 452 ($M^{\cdot+}$, 63) [Found: *m/z* (HRMS) 452.231 22. Calc. for $C_{26}H_{32}N_2O_5$: 452.231 12].

General methodology to evaluate yields for *ipso- vs. tele* substitution

To a solution of the isocolchicinoid (*ca.* 3 mg) in DMSO (0.15 cm^3) at room temp. was added neat piperidine (0.07 cm^3); formation of the piperidino derivatives **8/9** and disappearance of the starting substrate were followed by reversed-phase HPLC.

Kinetic measurements

The kinetics in dried DMSO were generally carried out by following the formation of the piperidino derivatives from an increase in the UV absorption at 430 nm (except for **18** which was at 440 nm) directly in a thermostatted spectrophotometric cuvette. Only for compounds **11** and **20** were the kinetics followed (up only 20–30% reaction completion) by HPLC for both disappearance of substrate and appearance of piperidino derivative.

Acknowledgements

We thank Mr A. Sterni for running the mass spectra and, for financial support, MURST (Progetti di Interesse Nazionale) and CNR, Roma.

References

1 G. Biggi, F. Del Cima and F. Pietra, *J. Am. Chem. Soc.*, 1973, **95**, 7101.
2 G. Biggi, A. J. de Hoog, F. Del Cima and F. Pietra, *J. Am. Chem. Soc.*, 1973, **95**, 7108.
3 F. Pietra, *Acc. Chem. Res.*, 1979, **12**, 132.
4 M. Cavazza, G. Morganti, C. A. Veracini, A. Guerriero and F. Pietra, *Tetrahedron Lett.*, 1982, 4115.
5 G. Biggi, F. Del Cima and F. Pietra, *Tetrahedron Lett.*, 1973, 183.
6 M. Cavazza, C. A. Veracini and F. Pietra, *J. Chem. Soc., Perkin Trans.* 2, 1992, 2201.
7 L. Velluz and G. Muller, *Bull. Soc. Chim. Fr.*, 1955, 198.
8 M. Cavazza and F. Pietra, *J. Chem. Soc., Chem. Comm.*, 1994, 897.
9 B. Danieli, G. Lesma, G. Palmisano and R. Riva, *Helv. Chim. Acta*, 1985, **68**, 2173.
10 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.
11 M. Cavazza and F. Pietra, *Tetrahedron Lett.*, 1995, **36**, 3429.
12 F. Pietra and F. Del Cima, *J. Chem. Soc.* B, 1971, 2224.
13 M. Cavazza, M. P. Colombini, M. Martinelli, L. Nucci, L. Pardi, F. Pietra and S. Santucci, *J. Am. Chem. Soc.*, 1977, **99**, 5997.
14 F. Pietra, M. Giocasta and F. Del Cima, *Tetrahedron Lett.*, 1969, 5097.
15 M. Cavazza and F. Pietra, *J. Chem. Soc., Perkin Trans. 1*, 1982, 1865.

Paper 5/02593A
Received 24*th April* 1995
Accepted 30*th May* 1995