Synthesis and chiroptical properties of pseudocolchicine and neocolchicine, novel unnatural regioisomers of colchicine

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Two novel regioisomers of colchicine **1**, pseudocolchicine ((*R*$_a$,7*S*)-*N*-(1,2,3,11-tetramethoxy-10-oxo-5,6,7,10-tetrahydrobenzo[*a*]heptalen-7-yl)acetamide **11**) and neocolchicine ((*R*$_a$,7*S*)-*N*-(1,2,3,10-tetramethoxy-11-oxo-5,6,7,11-tetrahydrobenzo[*a*]heptalen-7-yl)acetamide **13**), were obtained from 10-hydroxyneocolchicide **15** by either treatment with CH_2N_2followed by HPLC separation, or treatment with tosyl chloride followed by TLC separation of the resulting tosylates **16** and **17** and their regiospecific methoxylation with $Ti(OMe)_4$. The observation of similar UV and CD spectra for **11** and **13**, and for colchicine **1** and isocolchicine **6**, allowed us to come to a far reaching rationalisation of the electronic spectral behaviour of colchicinoids.

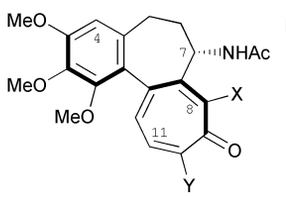
Introduction

The cycloheptatrienone nucleus bearing a nucleofuge shows complex behaviour towards nucleophiles. Besides *ipso* substitution of the nucleofuge, attack at other cycloheptatrienone carbons has been observed, followed by either protonation and elimination of the nucleofuge or ring contraction to a benzenoid derivative.[1]

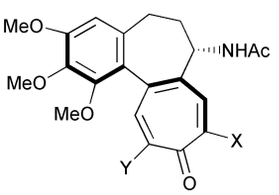
This dual behaviour was also observed for the cycloheptatrienone nucleus incorporated into the colchicinoids, although fusion into a tricyclic structure restricted the possible reaction modes.[2] A case-in-point is the reaction of isocolchicine **6**—an unnatural isomer of colchicine **1**—with sodium methanethiolate in aqueous methanol, by which Velluz and Muller originally obtained two products. The minor product was described as 9-methylthioisocolchicide **7**, while no structure was assigned to the main product, called pseudothiocolchicine.[3] The structure of the latter, 11-methylthioisocolchicide, was elucidated thirty years later.[4]

In the next decade, appraisal of the stereochemistry of colchicinoids (pseudothiocolchicine being subsequently described as (*R*$_a$,7*S*)-*N*-(1,2,3-trimethoxy-10-oxo-11-methylthio-5,6,7,10-tetrahydrobenzo[*a*]heptalen-7-yl)acetamide **10**), and clarification of Velluz and Muller's process,[3] allowed us to carry out the refunctionalization of 9-substituted isocolchicides at C(11) with amines and thiolates, and obtain the novel series of 11-amino and the 11-alkyl(aryl)thio colchicinoids.[2,5,6] Interestingly, 11-substituted isocolchicides exist as stable and isolatable (*R*$_a$,7*S*)- and (*S*$_a$,7*S*)-atropisomers, which allowed us to record for the first time dichroic spectra of atropisomeric colchicinoids bearing the natural acetylamino group at C(7).[7] Previously described atropisomeric colchicinoids suffered from either the presence of an anchoring group[8] at C(7) or the removal of the C(7) functionality.[9] Further still from our true atropisomeric colchicinoids are those cases in which the central ring is enlarged.[10]

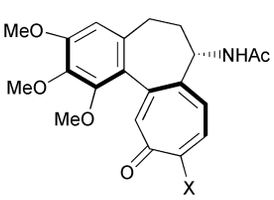
The existence of atropisomers may have a bearing on the behaviour of colchicine towards tubulin, although this is still awaiting full clarification.[7] Help with respect to this may be expected from the examination of the chemical and biological behaviour of other regioisomers of colchicine besides the known isocolchicine. Two of these regioisomers are described here together with their UV and CD spectra: pseudocolchicine ((*R*$_a$,7*S*)-*N*-(1,2,3,11-tetramethoxy-10-oxo-5,6,7,10-tetrahydrobenzo[*a*]heptalen-7-yl)acetamide **11**), which is the prototype of the C(11) functionalized series, and neocolchicine ((*R*$_a$,7*S*)-*N*-(1,2,3,10-tetramethoxy-11-oxo-5,6,7,11-tetrahydrobenzo[*a*]-heptalen-7-yl)acetamide, **13**), which is the prototype for a new class of colchicinoids.



(*R*$_a$,7*S*)-**1** X=H, Y=OMe
(*R*$_a$,7*S*)-**2** X=H, Y=NH_2
(*R*$_a$,7*S*)-**3** X=H, Y=SMe
(*R*$_a$,7*S*)-**4** X=H, Y=OTs
(*R*$_a$,7*S*)-**5** X=NH_2, Y=H



(*R*$_a$,7*S*)-**6** X=OMe, Y=H
(*R*$_a$,7*S*)-**7** X=SMe, Y=H
(*R*$_a$,7*S*)-**8** X=NH_2, Y=H
(*R*$_a$,7*S*)-**9** X=OTs, Y=H
(*R*$_a$,7*S*)-**10** X=H, Y=SMe
(*R*$_a$,7*S*)-**11** X=H, Y=OMe
(*R*$_a$,7*S*)-**12** X=H, Y=NH_2



(*R*$_a$,7*S*)-**13** X=OMe
(*R*$_a$,7*S*)-**14** X=NH_2

Results and discussion

It is known that both colchicine **1** and isocolchicine **6** react with aqueous ammonia at room temperature to give in high yield the *ipso*-substitution products, 10-aminocolchicide **2** and 9-aminoisocolchicide **8** respectively.[11] We observed the same behaviour

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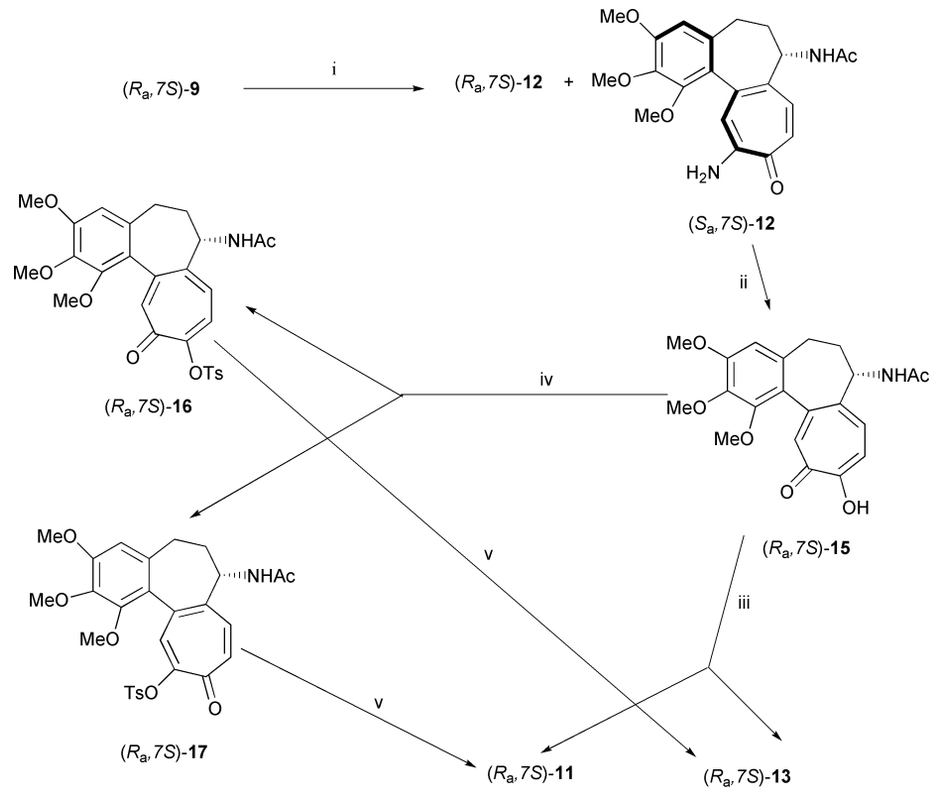


Scheme 1 *Reagents and conditions*: i, NH_3 liq., −25 °C; ii, KOH (2 M), EtOH, H_2O, 130 °C; iii, CH_2N_2, Et_2O, CH_2Cl_2; iv, $C_7H_7SO_2Cl$, py, rt; v, $Ti(OMe)_4$, MeOH, 105 °C.

for **1** and **6** in liquid ammonia as solvent at −25 °C .[7] In contrast, 9-tosyloxyisocolchicide (R_a,7*S*)-**9** gives a product of *tele*-substitution, 11-aminoisocolchicide **12**, as a mixture of (R_a,7*S*)- and (S_a,7*S*)-atropisomers. Although these could be separated into components[7] suitable for the synthesis of the target compounds **11** and **13**, the mixture also proved to be adequate in achieving this end (Scheme 1).

The regiospecific C(11) *tele*-substitution by NH_3 with **9** (Scheme 1) may be attributed to two concurrent causes: *i*) the presence, in the cycloheptatrienone ring of **9**, of a good nucleofuge and moderately activating group, like OTs, and ii) the low basicity and high H-nucleophilicity of ammonia.[2,12] That the atropisomeric mixture of **12** undergoes hydrolysis in ethanolic–aqueous KOH, under the drastic Eschenmoser's conditions,[13] to give 10-hydroxyneocolchicide **15** (Scheme 1), can be imputed to the amide-like behaviour of **12** towards bases.

Pseudocolchicine **11** and neocolchicine **13** could be obtained as a 1 : 1.7 mixture by treating 10-hydroxyneocolchicide **15** with diazomethane, albeit *via* a troublesome chromatographic separation that required HPLC procedures under reversed phase conditions (see Experimental section). It proved simpler to convert **15** with tosyl chloride in pyridine under standard conditions[14] to the tosyloxy derivatives **16** and **17**, which were easily separated by TLC (Scheme 1); regiospecific methoxylation of **16** and **17** with $Ti(OMe)_4$ in MeOH gave the target compounds **11** and **13**. It should be noted that this reaction required more drastic conditions, and gave lower yields, than with the use of the higher titanium alkoxides, $Ti(OR)_4$–ROH (R = Et, Pr^i, Bu).[15,16]

With both **11** and **13** a comparison could be carried out with the electronic absorption and CD spectra of colchicine **1** and isocolchicine **6**. The UV and CD spectra are similar for **11** and **13**, and for **1**[11,17,18] and **6**[11], while the spectral differences between the two pairs of compounds are remarkable. Thus, the intense absorption band centered at 310 nm for compounds **11** and **13** (ε *ca.* 10 000 dm^3 mol^{-1} cm^{-1}, Fig. 1, curves b and a, respectively), lies just where **1** and **6** show a weak absorption

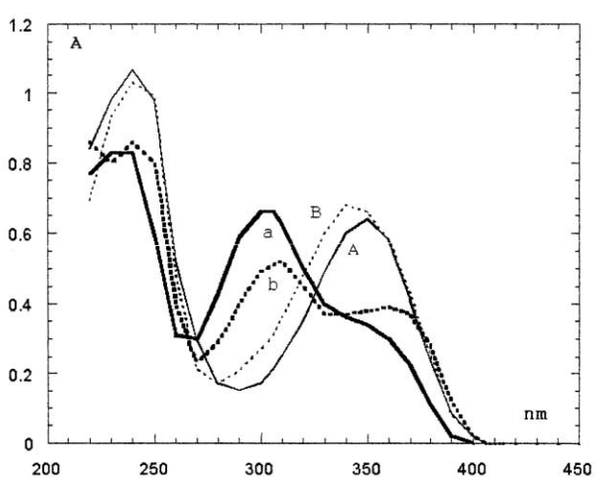
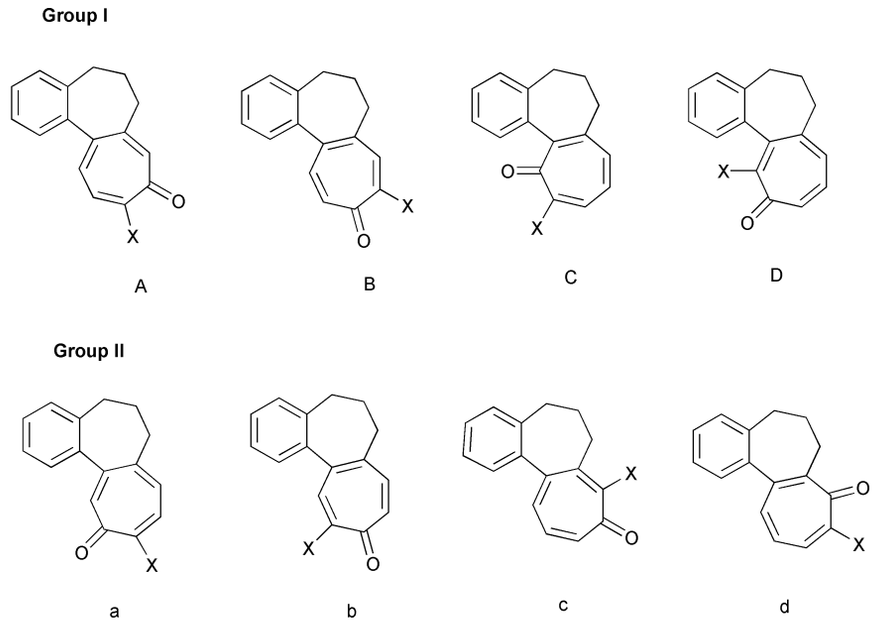


Fig. 1 *UV spectra*: a, (R_a,7*S*)-**13**; b, (R_a,7*S*)-**11**; A, (R_a,7*S*)-**1**; B, (R_a,7*S*)-**6**; EtOH, 4×10^{-5} mol dm^{-3}.

(ε *ca.* 1000, Fig. 1, curves A and B, respectively). The corresponding CD spectra reflect the above presence/absence of the absorption band at 310 nm (Fig. 2), implying vast electronic differences between the above two pairs of regioisomers.† Similar observations concerning the UV and CD spectra apply to the corresponding pairs of tosylates **4**[14],**9**[14] and **16**,**17** (see Experimental section).

This spectral behaviour can be rationalized by imagining eight possible colchicinoids (Scheme 2, where the 1-, 2-, 3-methoxy, and 7-acetylamino groups are ignored, being

† The signs of the dichroic bands indicate that the helicity of both **11** and **13** is the same for **1** and **6**, that is (R_a)[19] (see Fig. 2). The *J* coupling pattern for 7-H is another criterion used in assigning the helicity of colchicinoids.[7] This proton in both **11** and **13** appears as a td (see Experimental section), while the (S_a) helicity is characterized by a dd signal for the 7-H proton.[7]



Scheme 2

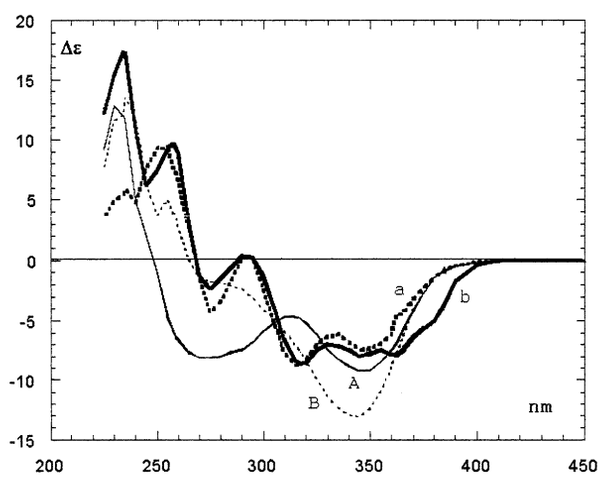


Fig. 2 *Dichroic spectra*: a, (R_a,7*S*)-**13**; b, (R_a,7*S*)-**11**; A, (R_a,7*S*)-**1**; B, (R_a,7*S*)-**6**; EtOH.

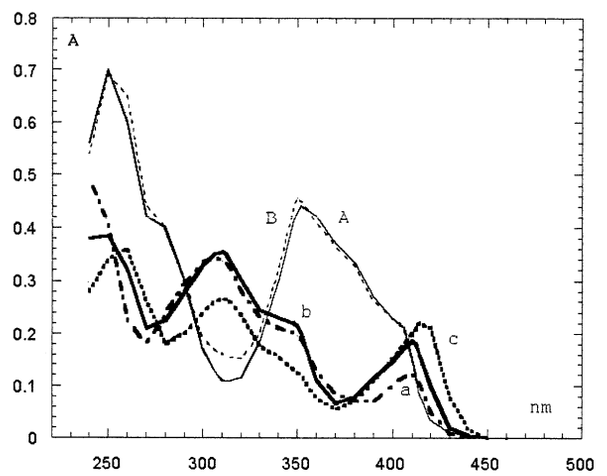


Fig. 3 *UV spectra*: a, (R_a,7*S*)-**14**; b, (R_a,7*S*)-**12**; c, (R_a,7*S*)-**5**; A, (R_a,7*S*)-**2**; B, (R_a,7*S*)-**8**; EtOH; a, b, c: 2×10^{-5} mol dm^{-3}; A, B: $3 \cdot 10^{-5}$ mol dm^{-3}.

irrelevant to our reasoning). These colchicinoids can be divided into two groups of four. Group I comprises all cases (A, B, C, D) where the aryl ring feels a perturbation from substituent X through the cycloheptatrienone system. Group II comprises all cases (a, b, c, d) where the X substituent cannot have that interaction mode with the aryl ring. It can be observed that compounds **1** and **6** correspond to formulae A and B, respectively, of group I (X = OMe), while **11** and **13** correspond to formulae b and a, respectively, of group II (X = OMe). Compounds **4** and **9** correspond to formulae A and B (group I, X = OTs), while **16** and **17** correspond to a and b (group II, X = OTs).

If the above classification is meaningful (that is if the perturbation induced on the aryl system by the substituent X on the cycloheptatrienone ring plays an important role in determining the spectral features of the colchicinoids), compound **5**,[7] which corresponds to formula c, in group II (X = NH_2), should show an UV spectrum similar to those of compounds **14**‡ and **12** (a and b, respectively, in group II, X = NH_2, Scheme 2). This is observed experimentally, as shown by Fig. 3, and the close matching of the UV spectra for compounds **2** and **8**,[11] correspond to A and B respectively, group I, X = NH_2 (Scheme 2).§

Similar observations were made for the corresponding alkylamino[2,7] and alkyl(aryl)thio[6] derivatives which warrant similar conclusions. It should be appreciated that this rationalization applies to all colchicinoids so far examined (A, B, a, b and c, Scheme 2), even if their arene and cycloheptatrienone rings are not coplanar. Whether the missing cases C, D and d (Scheme 2) fit our rationalization depends upon their synthesis. Admittedly, steric hindrance of the arene ring due to the carbonyl group in C or the X group in D, as an additional factor, may further increase the dihedral angle between the two rings so that conjugation of the X group with the arene ring does not occur at all.

‡ The UV spectrum of **14** was obtained by treating 2×10^{-5} mol dm^{-3} ethanolic solution of **13** with aq. NH_3 in excess in a UV cuvette. This spectrum was registered after 3 days at rt.

§ The band at 330 nm in the UV spectrum of pseudothiocolchicine **10**[4] (formula b, X = SMe, group II, Scheme 2) in comparison to the similar spectra of both thiocolchicine **3**[20] and isothiocolchicide **7**[4] (formulae A and B respectively, X = SMe, group I, Scheme 2, bands centered at *ca.* 380 nm), was earlier attributed to the lack of conjugation between the free electron pair of the S-atom at C(11) and the tropone π system due to steric hindrance by the MeO group at C(1).[4] Our molecular mechanics calculations rule out such a possibility.

Experimental

Mps were measured on a Kofler apparatus and are uncorrected. UV-visible spectra were recorded on a Perkin–Elmer Hitachi 200 instrument. CD spectra were recorded on a Jasco J-40AS spectrometer. IR spectra were measured on a Perkin-Elmer 1725X FT-IR spectrometer. ^{1}H NMR spectra at 200 MHz and ^{13}C NMR spectra at 50 MHz were determined on a Varian BB200, using deuteriochloroform solutions (tetramethylsilane as the internal reference). *J*-Values are given in Hz. Mass spectra were taken on a Kratos MS 80 spectrometer. TLC: preparative 20 × 20 cm silica gel Analtech plates. Reversed-phase HPLC: Spherisorb RP18 25 × 0.8 cm, flux 3 cm^3 min^{-1}. Reaction yields were not optimised.

Synthesis of (R_a,7*S*)-12 and (S_a,7*S*)-12[7]

Liquid ammonia (*ca.* 10 g) was added at −25 °C to 9-tosyloxyisocolchicide **9**[14] (0.244 g, 0.452 mmol) in a 50 cm^3 Hastelloy bomb. The temperature was allowed to rise to rt over 6 h. The semisolid residue obtained after evaporation of the ammonia was taken up with dichloromethane and filtered. Evaporation of the solvent gave a 1 : 1.7 mixture of (S_a,7*S*)-**12** and (R_a,7*S*)-**12** (0.136 g, 0.354 mmol, overall yield 78%) as yellow semisolid material. Initially, this was subjected to HPLC (eluant MeCN–H_2O 1 : 4), to give (S_a,7*S*)-**12** and (R_a,7*S*)-**12** at t_R 22.5 and 26 min respectively. The process was repeated more conveniently without separating the two atropisomers.

Data for (R_a,7*S*)-**12**: λ_{max}(EtOH)/nm 410 (log ε/dm^3 mol^{-1} cm^{-1} 3.87), 309 (4.12), 247 (4.15); δ_H ($CDCl_3$) 7.41 (1H, d, $J_{8,9}$ 12.4, 8-H), 7.20 (1H, d, $J_{9,8}$ 12.4, 9-H), 7.12 (1H, s, 12-H), 6.80 (1H, d, $J_{NH,7}$ 6.2, NH), 6.64 (1H, s, 4-H), 6.0 (2H, br s, NH_2), 4.60 (1H, td, $J_{7,NH}$ 6.2, $J_{7,pro\text{-}R\text{-}6}$ 5.3, $J_{7,pro\text{-}S\text{-}6}$ 12.2, 7-H), 3.94 (3H, s, 2-OMe), 3.90 (3H, s, 3-OMe), 3.63 (3H, s, 1-OMe), 2.6–2.2 (2H, m, 5-H), 2.2–1.8 (2H, m, 6-H), 2.04 (3H, s, COMe); δ_C ($CDCl_3$) 175.5 (s), 169.9 (s), 154.7 (s), 153.7 (s), 151.0 (s), 143.3 (s), 142.0 (s), 135.7 (s), 134.9 (s), 132.3 (d), 130.0 (d), 127.2 (s), 118.1 (d), 107.5 (d), 61.9 (q), 56.4 (q), 51.8 (d, C-7), 38.6 (t), 30.4 (t), 23.4 (q); *m*/*z* (EI) 384.1 (M^+, 11.5), 356.1 (M − CO, 18.5), 368.2 (M − NH_2, 0.6) (HRMS: found M^+ 384.16829 ± 0.00023. $C_{21}H_{24}N_2O_5$ requires 384.16852).

Data for (S_a,7*S*)-**12**: λ_{max}(EtOH)/nm 409 (log ε/dm^3 mol^{-1} cm^{-1} 3.81), 311 (4.06), 250 (4.12); δ_H ($CDCl_3$) 7.37 (1H, d, $J_{8,9}$ 12.1, 8-H), 7.14 (1H, d, $J_{9,8}$ 12.1, 9-H), 7.02 (1H, s, 12-H), 4.97 (1H, d, $J_{7,NH}$ 7.0, NH), 6.65 (1H, s, 4-H), 5.95 (2H, br s, NH_2), 5.03 (1H, dd, $J_{7,NH}$ 7.0, $J_{7,pro\text{-}R\text{-}6}$ 7.1, 7-H), 3.95 (3H, s, 2-OMe), 3.93 (3H, s, 3-OMe), 3.61 (3H, s, 1-OMe), 2.7–2.4 (2H, m, H-5), 2.2–1.8 (2H, m, H-6), 1.63 (3H, s, COMe); δ_C ($CDCl_3$) 175.9 (s), 168.2 (s), 154.7 (s), 154.1 (s), 151.0 (s), 143.5 (s), 140.1 (d), 135.5 (d), 135.4 (s), 130.3 (d), 128.5 (d), 118.4 (d), 107.6 (d), 61.6 (q), 56.4 (q), 55.4 (d, C-7), 40.8 (t), 30.4 (t), 23.5 (q); *m*/*z* (EI) 384.1 (M^+, 6.4) 356.1 (M − CO, 10.0), 368.2 (M − NH_2, 0.5) (HRMS: found M^+ 384.16826 ± 0.00026. $C_{21}H_{24}N_2O_5$ requires 384.16852).

Synthesis of (R_a,7*S*)-*N*-(10-hydroxy-1,2,3-trimethoxy-11-oxo-5,6,7,11-tetrahydrobenzo[*a*]heptalen-7-yl)acetamide, 10-hydroxyneocolchicide, 15

A mixture of (R_a,7*S*)-**12** and (S_a,7*S*)-**12** (0.537g, 1.39 mmol), was dissolved in 20 cm^3 EtOH and 20 cm^3 KOH (2 M) were added under N_2. The resulting solution was heated at 130 °C for 20 h. The cooled reaction mixture was acidified with dilute H_2SO_4 and extracted into chloroform. Evaporation of the dried organic extract, gave 0.213 g (0.55 mmol, 39.7% yield) of a light brown solid which was used without any further purification. Mp 119–125 °C (Found C, 65.6; H, 6.10. $C_{21}H_{23}NO_6$ requires C, 65.44; H, 6.01%); λ_{max}(EtOH)/nm 308 (log ε/dm^3 mol^{-1} cm^{-1} 4.20), 385 sh, 366 sh, 345 sh; ν_{max} (Nujol)/cm^{-1} 1653, 1595, 1541; δ_H ($CDCl_3$) 7.54 (1H, s, 12-H), 7.52 (1H, d, *J* 10.2, 9-H), 7.35 (1H, d, *J* 10.2, 8-H), 6.54 (1H, s, 4-H), 6.2 (1H, br d, NH), 4.62 (1H, m, 7-H), 3.94, 3.91 and 3.66 (9H, three s, 1-, 2- and 3-OMe), 2.6–2.2 (2H, m, 5-H), 2.2–1.8 (2H, m, 6-H), 2.03 (3H, s, MeCO); δ_C ($CDCl_3$) 173.5, 169.6, 153.9, 151.2, 144.7, 140.5, 134.4, 132.9, 126.8, 125.6, 107.4, 61.8, 56.5, 52.5, 38.7, 30.3, 23.6; *m*/*z* (EI) 385 (M^+, 85), 357 (M − CO, 90), 342 (M − Ac, 37), 314 (M − CO − Ac, 44), 298 (M − CO − $AcNH_2$, 30).

Synthesis of (R_a,7*S*)-toluene-4-sulfonic acid 7-acetylamino-1,2,3-trimethoxy-11-oxo-5,6,7,11-tetrahydrobenzo[*a*]heptalen-10-yl ester, (R_a,7*S*)-16 and (R_a,7*S*)-toluene-4-sulfonic acid 7-acetylamino-1,2,3-trimethoxy-10-oxo-5,6,7,10-tetrahydrobenzo[*a*]heptalen-11-yl ester, (R_a,7*S*)-17

10-Hydroxyneocolchicide **15** (0.213 g, 0.55 mmol) was stirred with 0.115 g, (0.6 mmol) of toluene-*p*-sulfonyl chloride in dry pyridine (0.5 ml) for 24 h at rt. The reaction mixture was diluted with H_2O and extracted with $CHCl_3$. The organic extracts were washed with H_2O and dried with Na_2SO_4 and evaporated under vacuum to give a yellow semisolid mass which was treated by TLC ($CHCl_3$–MeCOMe 3 : 2). Extraction of a band at R_f = 0.61 gave 0.065g (0.12 mmol, 22% yield) of (R_a,7*S*)-**16** as a yellow solid, mp 105–107 °C, while extraction of the spot at R_f = 0.40 gave 0.058g (0.11 mmol, 20% yield) of (R_a,7*S*)-**17** as a yellow solid, mp 110–113 °C.

Data for (R_a,7*S*)-**16**: (Found C, 62.1; H, 5.3. $C_{28}H_{29}NO_8S$ requires C, 62.33; H, 5.42%); CD (in EtOH)/nm ($\Delta\varepsilon$/dm^3 mol^{-1} cm^{-1}) 336 (−8.6), 300 (+2.0), 279 (−1.8), 244 (+16), 237 (+17.6); λ_{max}(EtOH)/nm 312 (log ε/dm^3 mol^{-1} cm^{-1} 4.08), 225 (4.43); ν_{max}(Nujol)/cm^{-1} 1654, 1626, 1593, 1559; δ_H ($CDCl_3$) 7.94 (2H, d, *J* 8.0, tosyl protons), 7.47 (1H, d, *J* 10.2, 9-H), 7.35 (2H, d, *J* 8.0, tosyl protons), 7.31 (1H, s, 12-H), 7.08 (1H, d, *J* 10.2, 8-H), 6.7 (1H, d, *J* 6.2, NH), 6.51 (1H, s, 4-H), 4.54 (1H, td, $J_{7,NH}$ 6.2, $J_{7,pro\text{-}R\text{-}6}$ 5.2, $J_{7,pro\text{-}S\text{-}6}$ 11.6, 7-H), 3.89 (6H, s, 2- and 3-OMe), 3.63 (3H, s, 1-OMe), 2.6–2.2 (2H, m, 5-H), 2.45 (3H, s, tosyl Me), 2.2–1.9 (2H, m, 6-H), 2.03 (3H, s, COMe); δ_C ($CDCl_3$) 177.8, 169.7, 154.1, 153.4, 150.2, 145.6, 144.9, 144.2, 133.8, 129.8, 129.0, 128.7, 123.6, 107.3, 61.8, 56.5, 52.7, 36.7, 30.2, 23.5, 22.3; *m*/*z* (EI) M^+ not observed, 385 (M − $C_7H_7SO_2$), 357 (M − $C_7H_7SO_2$ − CO).

Data for (R_a,7*S*)-**17**: (Found C, 62.21; H, 5.3. $C_{28}H_{29}NO_8S$ requires C, 62.33; H, 5.42%); CD (in EtOH)/nm ($\Delta\varepsilon$/dm^3 mol^{-1} cm^{-1}) 336(−13.6), 294 (+1.0), 254 (+8.4), 232 (+24.5); λ_{max}(EtOH)/nm 323 (log ε/dm^3 mol^{-1} cm^{-1} 4.13), 225 (4.55); ν_{max}(Nujol)/cm^{-1} 1654, 1624, 1595, 1560; δ_H ($CDCl_3$) 7.93 (2H, d, *J* 8.2, tosyl protons), 7.52 (1H, s, 12-H), 7.44 (1H, d, *J* 13.2, 8-H), 7.32 (2H, d, *J* 8.2, tosyl protons), 7.19 (1H, d, *J* 13.2, 9-H), 6.56 (1H, s, 4-H), 6.40 (1H, d, *J* 6.2, NH), 4.50 (1H, td, $J_{7,NH}$ 6.2, $J_{7,pro\text{-}R\text{-}6}$ 5.0, $J_{7,pro\text{-}S\text{-}6}$ 12, 7-H), 3.92 (3H, s, 2-OMe), 3.90 (3H, s, 3-OMe), 3.71 (3H, s, 1-OMe), 2.6–2.2 (2H, m, 5-H), 2.42 (3H, s, tosyl Me), 2.2–1.9 (2H, m, 6-H), 2.03 (3H, s, COMe); δ_C ($CDCl_3$) 178.5, 169.9, 154.4, 152.2, 151.1, 145.8, 145.3, 141.7, 139.5, 137.7, 135.4, 135.1, 133.5, 129.7, 128.6, 125.0, 107.7, 62.0, 61.8, 56.6, 52.6, 39.0, 30.3, 23.5, 22.3; *m*/*z* (EI) M^+ not observed, 385 (M − $C_7H_7SO_2$), 357 (M − $C_7H_7SO_2$ − CO).

Synthesis of (R_a,7*S*)-11 and (R_a,7*S*)-13

Excess CH_2N_2 in ether was added to a solution of 0.100 g of **15** (0.26 mmol) in 2 cm^3 of methylene chloride. After 1 h at rt the solvent was evaporated and the residue subjected to HPLC (MeCN–H_2O 3 : 7). Two fractions were collected: fraction with t_R = 6.5 min gave **13** 0.034 g (0.086 mmol, 33% yield), while the fraction with t_R = 7.0 min gave **11** (0.058 g, 0.15 mmol, 57% yield).

Data for (R_a,7*S*)-*N*-(1,2,3,11-tetramethoxy-10-oxo-5,6,7,10-tetrahydrobenzo[*a*]heptalen-7-yl)acetamide **11**: colourless solid, mp 97–101 °C; λ_{max} (EtOH)/nm 380 sh, 362 sh, 348 sh, 308 (log ε/dm^3 mol^{-1} cm^{-1} 4.11), 244 (4.33); ν_{max}(Nujol)/cm^{-1} 1655, 1617, 1596, 1554; δ_H ($CDCl_3$) 7.40 (1H, d, *J* 12.2, 8-H), 7.27 (1H, d, *J* 12.2, 9-H), 7.06 (1H, s, 12-H), 6.61 (1H, s, 4-H), 6.16 (1H, d, *J* 6.0, NH), 4.60 (1H, td, $J_{7,NH}$ 6.0, $J_{7,pro\text{-}R\text{-}6}$ 6.6, $J_{7,pro\text{-}S\text{-}6}$

12, 7-H), 3.98 (3H, s, 2-OMe), 3.94 (3H, s, 3-OMe), 3.92 (3H, s, 11-OMe), 3.70 (3H, s, 1-OMe), 2.6–2.2 (2H, m, 5-H), 2.2–1.8 (2H, m, 5-H), 2.06 (3H, s, COMe); δ_C ($CDCl_3$) 179.6, 169.6, 162.5, 154.1, 151.3, 141.8, 139.4, 138.8, 135.9, 135.0, 132.7, 118.4, 107.7, 62.2, 61.8, 56.6, 39.0, 30.5, 23.6; *m*/*z* (EI) 399.1 (M^+, 11.3%), 371 (M − CO, 8.4), 356 (M − Ac, 4.3), 340 (M − $AcNH_2$, 12.7), 328 (M − CO − Ac, 4.0), 312 (M − CO − $AcNH_2$, 4.5) (HRMS: found M^+ 399.16735 ± 0.00084. $C_{22}H_{25}NO_6$ requires 399.16819).

Data for (*R*$_a$,7*S*)-*N*-(1,2,3,10-tetramethoxy-11-oxo-5,6,7,11-tetrahydrobenzo[*a*]heptalen-7-yl)acetamide **13**: colourless solid, mp 227–230 °C; λ_{max}(EtOH)/nm 372 sh, 360 sh, 348 sh, 302 (log ε/dm^3 mol^{-1} cm^{-1} 4.20), 236 (4.31); ν_{max}(Nujol)/cm^{-1} 1667, 1612, 1581, 1526; δ_H ($CDCl_3$) 7.45 (1H, s, 12-H), 7.16 (1H, d, *J* 10.9, 9-H), 6.83 (1H, d, *J* 10.9, 8-H), 6.60 (1H, d, *J* 5, NH), 6.51 (1H, s, 4-H), 4.56 (1H, td, $J_{7,NH}$ 5.0, $J_{7,pro\text{-}R\text{-}6}$ 6, $J_{7,pro\text{-}S\text{-}6}$ 12.4, 7-H), 3.96 (3H, s, 2-OMe), 3.90 (6H, s, 3- and 10-OMe), 3.63 (3H, s, 1-OMe), 2.6–2.2 (2H, m, 5-H), 2.2–1.8 (2H, m, 6-H), 2.04 (3H, s, COMe); δ_C ($CDCl_3$) 178.8, 169.5, 163.9, 154.0, 151.0, 144.8, 141.6, 140.3, 133.8, 125.4, 112.6, 107.2, 61.7, 56.5, 52.3, 37.3, 30.3, 23.6; *m*/*z* (EI) 399.1 (M^+, 11.9%), 371 (M − CO, 26.6), 356 (M − Ac, 7.7), 340 (M − $AcNH_2$, 8.2), 328 (M − CO − Ac, 8.5), 312 (M − CO − $AcNH_2$, 30.8) (HRMS: found M^+ 399.16757 ± 0.00062. $C_{22}H_{25}NO_6$ requires 399.16819).

Synthesis of (*R*$_a$,7*S*)-13

To a solution of (*R*$_a$,7*S*)-**16** (0.061 g, 0.113 mmol) in 4 cm^3 of MeOH, was added $Ti(OMe)_4$ (0.182 g, 1.0 mmol) under N_2. The mixture was heated for 6.5 h at 105 °C, then cooled, the solvent evaporated, and the residue treated with CH_2Cl_2 and filtered. Evaporation of CH_2Cl_2 gave a semisolid mass which was subjected to SiO_2 TLC with CH_2Cl_2–CH_3COCH_3 2 : 3. The R_f = 0.13 band gave **13** (0.020 g, 0.05 mmol, 44.3% yield).

Synthesis of (*R*$_a$,7*S*)-11

Starting from 0.048 g (0.089 mmol) of **17** in 3 cm^3 MeOH and 0.146 g (0.84 mmol) of $Ti(OMe)_4$, **11** (0.0064 g, 0.016 mmol, 18% yield) was obtained *via* the work up described in the previous case.

References

1 F. Pietra, *Acc. Chem. Res.*, 1979, **12**, 132.
2 M. Cavazza and F. Pietra, *J. Chem. Soc., Perkin Trans. I*, 1995, 2657.
3 L. Velluz and G. Muller, *Bull. Soc. Chim. Fr.*, 1955, 198.
4 B. Danieli, G. Lesma, G. Palmisano and R. Riva, *Helv. Chim. Acta*, 1985, **68**, 2173.
5 M. Cavazza and F. Pietra, *J. Chem. Soc., Chem. Commun.*, 1994, 897.
6 M. Cavazza and F. Pietra, *Z. Naturforsch., Teil B*, 1996, **51**, 1347.
7 M. Cavazza, M. Zandomeneghi and F. Pietra, *Tetrahedron Lett.*, 2000, **41**, 9129.
8 E. A. Pyles and S. Bane Hastie, *J. Org. Chem.*, 1993, **58**, 2751.
9 U. Berg, J. Deinum, P. Lincoln and J. Kvassman, *Bioorg. Chem.*, 1991, **19**, 53.
10 U. Berg, H. Bladh, C. Svensson and M. Wallin, *Bioorg. Med. Chem. Lett.*, 1997, **7**, 2771.
11 R. M. Horowitz and G. E. Ullyot, *J. Am. Chem. Soc.*, 1952, **74**, 587.
12 G. Biggi, F. Del Cima and F. Pietra, *J. Am. Chem. Soc.*, 1973, **95**, 7101.
13 J. Schreiber, W. Leimgruber, M. Pesaro, P. Schudel, T. Threlfall and A. Eschenmoser, *Helv. Chim. Acta*, 1961, **44**, 540.
14 M. E. Staretz and S. B. Hastie, *J. Org. Chem.*, 1991, **56**, 428.
15 M. Cavazza and F. Pietra, *Tetrahedron*, 1998, **54**, 14059.
16 P. Kouroupis, J. Kessler and H. J. Hansen, *Helv. Chim. Acta*, 1996, **79**, 208.
17 S. B. Hastie and R. Rava, *J. Am. Chem. Soc.*, 1989, **111**, 6993.
18 A. Brossi, O. Boyè, A. Muzaffar, H. J. C. Yeh, V. Toome, B. B. Wegrzynski and C. George, *FEBS Lett.*, 1990, **262**, 5.
19 U. Berg and H. Bladh, *Helv. Chim. Acta*, 1999, **82**, 323.
20 A. Muzaffar, A. Brossi, C. M. Lin and E. Hamel, *J. Med. Chem.*, 1990, **33**, 567.