20. 10-Alkyl-10-demethylcolchicines

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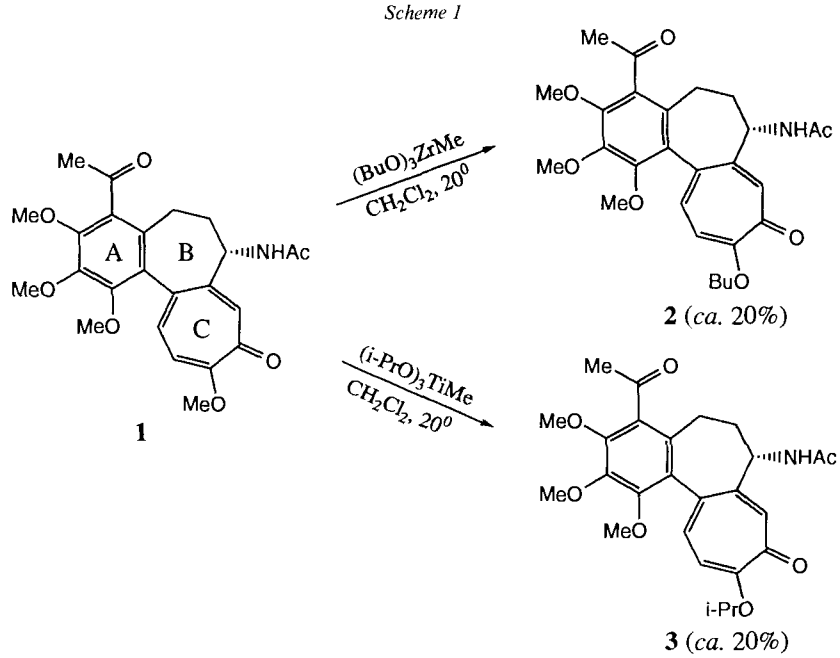
It is shown that colchicine (**4**) can regiospecifically be transetherified at C(10) by heating in ROH in the presence of $(RO)_4M$ (M = Ti, Zr; *cf. Scheme 2*). $(PrO)_4Zr$ in PrOH gives better yields than $(PrO)_4Ti$ in PrOH, and also in the catalytic variant of the conversion is $(PrO)_4Zr$ more effective than $(PrO)_4Ti$.

In the preceding paper, we described the synthesis of 4-acetylcolchicine (**1**) [1]. Our original idea was to use this compound as starting material for the synthesis of 4-(*tert*-butyl)colchicine. However, neither the dimethylation procedure for ketones, developed by *Reetz et al.* [2], nor the methylenations described by *Tebbe et al.* [3], *Tour et al.* [4] as well as by *Lombardo* [5] were successful in the case of **1**. It was also not possible to add alkylmagnesium or alkyllithium reagents to **1**. The X-ray crystal structure of **1** [1] shows the 4-Ac substituent in an almost orthogonal conformation with respect to the plane of

Scheme 1



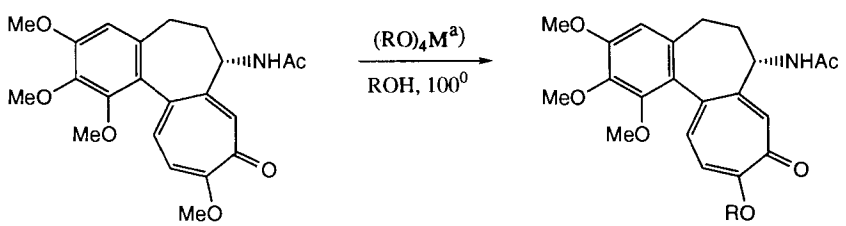
[1]) Part of the Ph.D. thesis of *P.K.*, University of Zurich, 1993.

the benzene ring, *i.e.*, the MeO group at C(3) as well as CH_2(5) of ring B of **1** seem to block the two possible paths for a nucleophilic attack upon the 4-Ac moiety. To verify this idea, we reacted **1** with $(BuO)_3ZrMe$ as well as with $(i\text{-}PrO)_3TiMe$ for which *Seebach* and coworkers had shown that they methylate ketones at temperatures above 0° [6]. Moreover, we have found that $(BuO)_3ZrMe$ methylates 4-formylcolchicine in good yields [7]. However, the reaction of **1** took another path, *i.e.*, no methylation occurred at the 4-Ac group. Instead, we observed the formation of the corresponding 10-butyl- and 10-isopropyl-10-demethylcolchicines, **2** and **3**, respectively, in decent yields (*Scheme 1*).

Nucleophilic exchange reactions at C(10) of colchicine (**4**) and of its derivatives have so far only been observed with soft nucleophiles such as MeS^-, leading to thiocolchicines, or amines, which form colchicinamides (*cf.* [8] and lit. cit. therein). Hard bases such as HO^- or RO^- normally induce contraction of ring C leading to corresponding allocolchicines (*cf.* [8])[2]). Therefore, we assumed that the regiospecific transetherification reaction of **1** at C(10) must follow a similar mechanism as the transesterification of simple carboxylic esters, which can be catalyzed by Ti- and Zr-alkoxides (*cf.* [6b] [9] and lit. cit. therein).

Indeed, when we reacted colchicine (**4**) with an excess of $(RO)_4Ti$ in the corresponding alcohol ROH as solvent, we observed in all cases a regiospecific exchange reaction of the MeO–C(10) group of **4** (*Scheme 2*). The presence of any isocolchicine derivatives could

Scheme 2



4 **5a–e**[b])

[a]) 1 mmol of **4** was reacted with 5 mmol of $(RO)_4M$ (M = Ti, Zr) in 10 ml of ROH under reflux or at 100° for 17 h (M = Ti) and for 2.5 h (M = Zr).

[b]) **5a**: R = Et (62%); **5b**: R = Pr (25% (M = Ti); 66% (M = Zr)); **5c**: R = i-Pr (85%); **5d**: R = Bu (29%); **5e**: R = 2-Ethylhexyl (14%).

be excluded on the basis of the ^{1}H-NMR spectra of the new colchicines **5** which showed for the substituents at the colchicine skeleton almost identical chemical shifts and coupling constants as compared to **4**. The reaction of **4** with 5 mol-equiv. of $(i\text{-}PrO)_4Ti$ could also be realized in MeCN (57%), PhMe (41%), and dioxane (27%) as solvents (yields in parentheses); however, the yields of **5c** were distinctly lower than in i-PrOH (*cf.* [9]). The conversion of **4** with $(t\text{-}BuO)_4Ti$ in *t*-BuOH did not lead to the formation of 10-(*tert*-butyl)-10-demethylcolchicine. On the other hand, when **4** was reacted in BuOH in the presence of $(t\text{-}BuO)_4Ti$, only **5d** could be isolated in a yield of 12% (*cf.* [9]).

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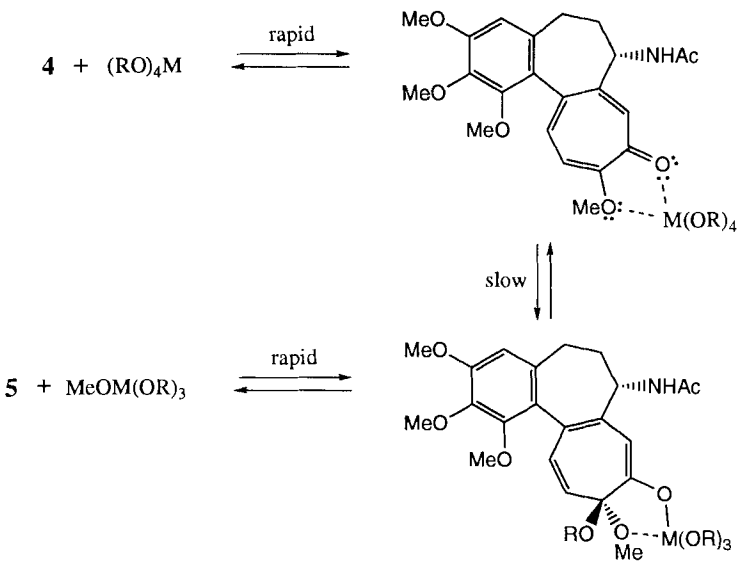
[2]) For mechanistic investigations on nucleophilic reactions of tropolones, see [9] (*cf.* also [10]).

We assume that the exchange reactions at **4** take place *via* complexation at the oxo group at C(9) followed by vinylogous addition of RO^- onto C(10) as it is generally observed in nucleophilic displacement reactions of tropolones and their derivatives (*Scheme 3*; *cf.* [10] [11]).

Scheme 3



This mechanistic view imposes that the exchange reaction of **4** should also be realizable with catalytic amounts of $(RO)_4M$ in ROH. This is indeed the case. The reaction of **4** with PrOH in the presence of 0.25 mol-equiv. of $(PrO)_4M$ led, after 8 h heating under reflux, to **5b** in yields of *ca.* 10% (M = Ti) and 63% (M = Zr). The higher reactivity of Zr-alkoxides as compared to Ti-alkoxides as well as of α-branched M-alkoxides as compared to unbranched M-alkoxides has already been observed in other alkoxide-transfer reactions (*cf.* [9]).

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Experimental Part

General. See [7].

Standard Procedure for the Synthesis of the 10-Alkyl-10-demethylcolchicines **5**. Colchicine (**4**; 0.400 g, 1.00 mmol) was dissolved in ROH (10 ml), $(RO)_4Ti$ or $(RO)_4Zr$ (5 mmol) was added and the mixture heated under reflux or at a maximum temp. of 100° for 17 h, if not otherwise stated. The yellow reaction mixture was poured into an ice-cooled aq. 20% KF soln. (30 ml) and stirred for 15 min. The mixture was extracted with CH_2Cl_2 (3 × 50 ml). The combined CH_2Cl_2 layers were washed with sat. aq. NaCl soln. and dried ($MgSO_4$). The raw product was chromatographed on silica gel (AcOEt/EtOH 7:3). The products **5** were obtained as pale-yellow foams, which tenaciously retained solvent molecules. Therefore, the foams were dried at 50°/high vacuum, until their weight did not change any more. The elemental analyses showed still too low C values after this procedure.

10-Ethyl-10-demethylcolchicine (**5a**). The reaction with $(EtO)_4Ti$ (*Fluka*; *ca.* 97%) gave **5a** (0.255 g) in a yield of 62%. R_f (AcOEt/EtOH 7:3) 0.40 (R_f (**4**) 0.28). $[\alpha]_{589}^{20} = -131.8$ ($c = 1.785$, $CHCl_3$). UV (99% EtOH): λ_{max} 350 (4.18), 242 (4.44), 237 (4.44); λ_{min} 292 (3.65), 239 (4.43). IR ($CHCl_3$): 3442*m* (NH; free), 3281*m* (br., NH; interm. bound), 3001*s*, 2939*m*, 1673*s*, 1614*s*, 1576*s*, 1557*s*, 1488*s*, 1464*s*, 1444*m*, 1433*m*, 1401*m*, 1374*m*, 1350*s*, 1322*s*, 1286*s*, 1248*s*, 1172*m*, 1143*s*, 1097*s*. ^{1}H-NMR (300 MHz, $CDCl_3$): 8.11 (*d*, $J = 6.4$, NH); 7.57 (*s*, H–C(8)); 7.29 (*d*, $J = 10.8$, H–C(12)); 6.85 (*d*, $J = 10.9$, H–C(11)); 6.51 (*s*, H–C(4)); 4.62 (2*t*, superimp., H–C(7)); 4.22 (*q*, $J = 7.0$, $MeCH_2O$); 3.92, 3.88, 3.63 (3*s*, 3 MeO); 2.5–1.9 (3*m*, CH_2(5,6)); 1.95 (*s*, *Me*CONH); 1.53 (*t*, $J = 7.0$, $MeCH_2O$). EI-MS: 413 (39, $M^{+\cdot}$), 398 (18, $[M - Me]^+$), 385 (24, $[M - CO(C_2H_4)]^{+\cdot}$), 370 (31, $[M - MeCO]^+$), 356 (23), 354 (25), 342 (11), 339 (17), 328 (11), 327 (32), 326 (100), 311 (30), 282 (30), 85 (77).

10-Demethyl-10-propylcolchicine (**5b**). The reaction with $(PrO)_4Ti$ (*Fluka*; *pract.*) gave **5b** (0.105 g) in a yield of 25%. The same reaction with $(PrO)_4Zr$ (*Fluka*; 70% in PrOH) for 2.5 h at reflux temp. gave **5b** (0.282 g) in a yield of 66%. R_f (AcOEt/EtOH 7:3) 0.41. $[\alpha]_{589}^{20} = -130.0$ ($c = 1.128$, $CHCl_3$). UV (99% EtOH): λ_{max} 350 (4.15), 242 (4.41), 237 (4.43); λ_{min} 296 (3.74), 239 (4.41). IR ($CHCl_3$): 3442*m* (NH; free), 3276*m* (br., NH; interm. bound), 3003*s*, 2939*m*, 2880*m*, 1671*s*, 1614*s*, 1585*s*, 1557*s*, 1488*s*, 1464*s*, 1433*m*, 1401*m*, 1368*m*, 1350*s*, 1322*s*, 1284*s*, 1248*s*, 1172*s*, 1143*s*, 1096*s*, 1049*m*. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.60 (*d*, $J = 6.6$, NH); 7.59 (*s*, H–C(8)); 7.29 (*d*, $J = 10.8$, H–C(12)); 6.85 (*d*, $J = 10.9$, H–C(11)); 6.52 (*s*, H–C(4)); 4.64 (2*t*, superimp., H–C(7)); 4.09 (small *m*, $EtCH_2O$); 3.93, 3.89, 3.64 (3*s*, 3 MeO); 2.5–2.2 (*m*, 3 H–C(5,6)); 1.97 (*s*, MeCONH); 2.0–1.8 (*m*, H–C(5), $MeCH_2CH_2O$); 1.06 (*t*, $J = 7.4$, $MeCH_2CH_2O$). EI-MS: 427 (43, $M^{+\cdot}$), 399 (37, $[M - CO]^{+\cdot}$), 398 (100, $[M - Et]^+$), 384 (14, $[M - MeCO]^+$), 368 (19), 357 (36), 356 (44), 340 (49), 283 (14), 282 (29).

10-Isopropyl-10-demethylcolchicine (**5c**). The reaction with $(i\text{-}PrO)_4Ti$ (*Fluka*; dest. under Ar) gave **5c** (0.364 g) in a yield of 85%. R_f (AcOEt/EtOH 7:3) 0.41. $[\alpha]_{589}^{20} = -120.5$ ($c = 1.091$, $CHCl_3$). UV (99% EtOH): λ_{max} 352 (4.18), 242 (sh, 4.43); λ_{min} 296 (3.75). IR ($CHCl_3$): 3442*m* (NH; free), 3277*m* (br., NH; intermol. bound), 3000*s*, 2938*m*, 1673*s*, 1614*s*, 1583*s*, 1557*s*, 1488*s*, 1464*s*, 1432*m*, 1401*m*, 1376*m*, 1350*s*, 1322*s*, 1283*s*, 1248*s*, 1172*s*, 1143*s*, 1070*s*. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.63 (*d*, $J = 6.7$, NH); 7.50 (*s*, H–C(8)); 7.27 (*d*, $J = 10.8$, H–C(12)); 6.87 (*d*, $J = 11.3$, H–C(11)); 6.51 (*s*, H–C(4)); 4.73 (*sept.*, $J = 6.1$, Me_2CHO); 4.63 (2*t*, superimp., H–C(7)); 3.92, 3.90, 3.64 (3*s*, 3 MeO); 2.5–2.2 (*m*, 3 H–C(5,6)); 1.96 (*s*, MeCONH); 1.90 (*m*, H–C(5)); 1.46, 1.45 (2*s*, Me_2CHO). EI-MS: 427 (17, $M^{+\cdot}$), 412 (8, $[M - Me]^+$), 399 (20, $[M - CO]^{+\cdot}$), 385 (29, $[M - CH_2CO]^{+\cdot}$), 369 (24, $[M - MeCONH]^+$), 357 (100), 342 (37), 314 (33), 298 (20), 283 (22), 282 (41). Anal. calc. for $C_{24}H_{29}NO_6$ (427.50): C 67.43, H 6.84, N 3.28; found: C 67.59, H 6.59, N 3.51.

The following yields of **5c** were realized, when the transetherification reaction was performed in MeCN: 57%, PhMe: 41%, and dioxane: 27% (19 h heating under reflux).

10-Butyl-10-demethylcolchicine (**5d**). The reaction with $(BuO)_4Ti$ (*Fluka*; *pract.*) gave **5d** (0.128 g) in a yield of 29%. R_f (AcOEt/EtOH 7:3) 0.37. $[\alpha]_{589}^{20} = -133.9$ ($c = 1.051$, $CHCl_3$). UV (99% EtOH): λ_{max} 352 (4.18), 242 (4.43), 237 (4.45); λ_{min} 297 (3.75), 239 (4.43). IR ($CHCl_3$): 3442*m* (NH; free), 3290*m* (br., NH; interm. bound), 3003*s*, 2963*m*, 2938*m*, 2875*m*, 1672*s*, 1614*s*, 1585*m*, 1557*s*, 1488*s*, 1464*s*, 1433*m*, 1401*m*, 1374*m*, 1350*s*, 1322*s*, 1285*s*, 1248*s*, 1172*s*, 1144*s*, 1096*s*, 1049*m*. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.46 (*s*, H–C(8)); 7.28 (*d*, $J = 10.8$, H–C(12)); 7.1 (br., NH); 6.84 (*d*, $J = 10.9$, H–C(11)); 6.53 (*s*, H–C(4)); 4.64 (2*t*, superimp., H–C(7)); 4.13 (small *m*, $PrCH_2O$); 3.93, 3.89, 3.64 (3*s*, 3 MeO); 2.5–2.2 (*m*, 3 H–C(5,6)); 1.98 (*s*, *Me*CONH); 2.0–1.7 (*m*, H–C(5), $EtCH_2CH_2O$); 1.52 (*sext.*-like, $MeCH_2CH_2CH_2O$); 0.99 (*t*, $MeCH_2CH_2CH_2O$). EI-MS: 441 (29, $M^{+\cdot}$), 413 (8, $[M - CO]^{+\cdot}$), 399 (27, $[M - CH_2CO]^{+\cdot}$), 398 (100, $[M - Pr(MeCO)]^+$), 382 (38), 357 (30), 356 (44), 355 (10), 354 (40), 311 (16), 283 (15), 282 (26).

10-(2-Ethylhexyl)-10-demethylcolchicine (**5e**). The reaction with (2-ethylhexyloxy)$_4$Ti (*Fluka*; *pract.*) gave **5e** (0.070 g) in a yield of 14%. R_f (AcOEt/EtOH 7:3) 0.40. $[\alpha]_{589}^{20} = -117.0$ ($c = 0.864$, $CHCl_3$). UV (99% EtOH): λ_{max} 349 (4.20), 242 (4.45), 234 (4.45); λ_{min} 292 (3.72), 239 (4.44). IR ($CHCl_3$): 3442*m* (NH; free), 3294*m* (br., NH; interm. bound), 3004*s*, 2963*s*, 2874*m*, 2861*m*, 1676*s*, 1616*s*, 1585*s*, 1563*s*, 1488*s*, 1464*s*, 1432*m*, 1401*m*, 1375*m*, 1350*s*, 1322*s*, 1284*s*, 1248*s*, 1172*s*, 1143*s*, 1096*s*, 1049*m*. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.67 (2*d*, $J = 7.1$, NH); 7.54 (*s*, H–C(8)); 7.27 (*d*, $J = 10.8$, H–C(12)); 6.83 (*d*, $J = 10.9$, H–C(11)); 6.52 (*s*, H–C(4)); 4.66 (2*t*, superimp., H–C(7)); 3.96 (small *m*, $BuCH(Et)CH_2O$); 3.93, 3.89, 3.65 (3*s*, 3 MeO); 2.5–2.2 (*m*, 3 H–C(5,6)); 1.97 (*s*, *Me*CONH); 2.0–1.8 (*m*, H–C(5), $BuCH(Et)CH_2O$); 1.6–1.3 (*m*, 8 aliph. H); 1.0–0.85 (small *m*, 2 aliph. Me). CI-MS (NH_3): 498 (100, $[M + 1]^+$), 398 (55), 385 (28), 357 (28).

Attempted Reaction of Colchicine (**4**) *with (t-BuO)$_4$Ti.* Colchicine (**4**; 0.248 g, 0.62 mmol) was heated under reflux in *t*-BuOH (10 ml) in the presence of (*t*-BuO)$_4$Ti (*Fluka, pract.*, 1.19 ml, 5 mmol) for 23 h. Colchicine was still present (TLC). Chromatographic workup yielded 0.016 g of product. ^{1}H-NMR showed that it consisted of a mixture of at least 3 colchicinoid compounds which were not further characterized.

However, when the typical run with **4** and $(t\text{-BuO})_4$Ti was performed in BuOH, **5d** (0.054 g) was obtained in a yield of 12% (*cf.* [9]).

Experiments with Catalytic Amounts of $(PrO)_4M$ *(M = Ti, Zr).* Colchicine (0.100 g, 0.25 mmol) and $(PrO)_4M$ (0.021 g (M = Ti) or 0.029 g (M = Zr), 0.0625 mmol) were dissolved in PrOH (5.0 ml) and heated under Ar and reflux for 1, 2, 4, and 8 h. With $(PrO)_4$Ti as catalyst, only after 8 h *ca.* 10% of **5b** could be detected by ^{1}H-NMR. The reaction mixtures with $(PrO)_4$Zr as catalyst showed the following composition according to ^{1}H-NMR: 1 h: < 10%, 2 h: 20%, 4 h: 34%, and 8 h: 63% of **5b**.

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