Tetrahedron Letters,Vol.29,No.38,pp 4839-4842,1988 0040-4039/88 $3.00 + .00
Printed in Great Britain Pergamon Press plc

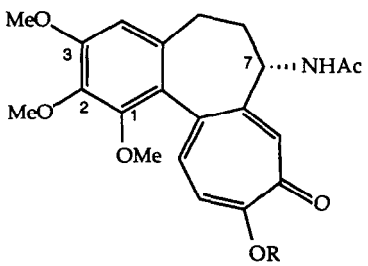
TOTAL SYNTHESIS OF (±)-N-ACETYLCOLCHINOL

J. Scott Sawyer[1] and Timothy L. Macdonald

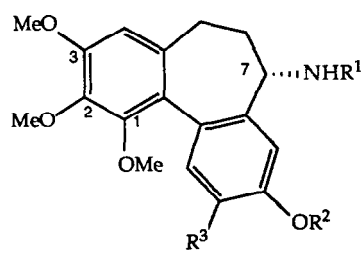
Department of Chemistry
University of Virginia
Charlottesville, VA 22901

Summary: An efficient synthesis of the colchicine degradation product N-acetylcolchinol 3 is described featuring a thallium(III)-mediated intramolecular non-phenolic biaryl oxidative coupling reaction of intermediate 12 as the key step. Both the synthetic sample and that obtained from the degradation of colchicine were found to exist in solution as a 3:1 mixture of conformational isomers at room temperature.

Current interest in the biological properties of the *Colchicum* alkaloids is evidenced by numerous recent reports concerning the synthesis and pharmacological evaluation of structural analogs of colchicine 1.[2,3] An interesting structure in this regard is the colchicine degradation product N-acetylcolchinol 3, first described by Windaus[4a] in 1914.



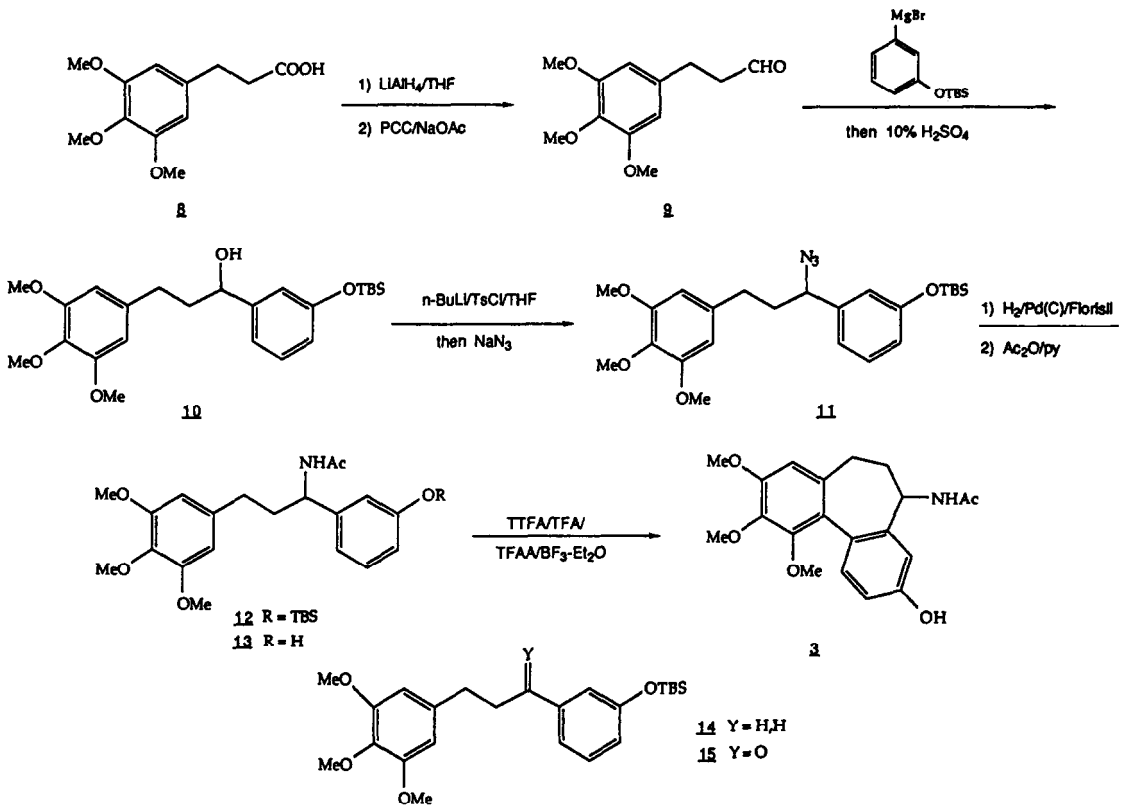
1 R = Me
2 R = H



3 R^1 = Ac, R^2,R^3 = H
4 R^1 = Ac, R^2 = H, R^3 = I
5 R^1 = Ac, R^2 = CH_2CH_2OH, R^3 = H
6 R^1,R^3 = H, R^2 = Me
7 R^1 = Ac, R^2 = Me, R^3 = H

Degradation proceeds by treatment of colchiceine 2 with hypoiodite producing the ring-contracted iodophenol 4, which is then reduced by zinc/acetic acid to give 3.[4] The action of basic hydrogen peroxide on colchiceine 2[4b] or hydrogen peroxide on colchicine 1[5] leads directly to N-acetylcolchinol 3.[6] Ethylene glycol has been used to mediate the contraction of the colchicine tropolone ring to afford the glycol ether 5.[7] In addition to degradative work from natural colchicine, the total syntheses of colchinol methyl ether 6[8] and (-)-N-acetylcolchinol methyl ether 7 have been reported.[9] This report describes the first total synthesis of (±)-N-acetylcolchinol and involves a concise route amenable to structural analogs.

Our approach centers on the thallium(III)-promoted non-phenolic biaryl coupling[10] of the protected 1-acetamido-1,3-diphenylpropane compound 12. We also envisioned key intermediate 12 providing ready access to the corresponding free phenol 13, an appropriate substrate for phenolic biaryl coupling methodology.[11] Construction of silylated 1-acetamido-1,3-diphenylpropane 12 began with the reduction of commercially available acid 8 to the corresponding alcohol followed by pyridinium chlorochromate oxidation to aldehyde 9 (80% overall yield from starting acid).[12] Addition of *m*-t-butyldimethylsilyloxyphenylmagnesium bromide to aldehyde 9 proceeded smoothly providing alcohol 10 in 96% yield after acid quench and purification. Introduction of the requisite nitrogen[13] at C-7 was achieved through benzylic azide 11, formed by the one-pot conversion of alcohol 10 into the corresponding tosylate and subsequent displacement with an excess of azide ion (81% yield).



Successful reduction of azide 11 was realized only after lengthy exploration of the many methods reported in the literature.[14] Most conditions examined resulted in either recovered starting material or the benzylic cleavage product 14. This impasse was circumvented by hydrogenolysis of 11 over 5% palladium-on-carbon in the presence of Florisil to provide the corresponding amine in reproducible yields. Acylation proceeded uneventfully to give 1-acetamido-1,3-diphenylpropane 12 (50-60% from 11). Without Florisil (believed to limit the amine's accessibility to the catalyst) the major product was the reduced compound 14.

Treatment of a 20:1 v/v trifluoroacetic acid (TFA)/trifluoroacetic anhydride (TFAA) solution of 1-acetamido-1,3-diphenylpropane 12 (4.0 millimolar) with 1.1 molar equivalents thallium(III) trifluoroacetate (TTFA) in the presence of freshly distilled boron trifluoride etherate (4.5 ml/mmol 12) at 0°C for 4 hours resulted in a dark oil which after column chromatography gave (±)-N-acetylcolchinol 3[15] as off-white needles in 71% yield. The obvious possibility of initial desilylation of 12 to the free phenol 13 was addressed to ascertain the nature of the cyclization, i.e., phenolic or non-phenolic. Desilylation of 12 to phenol 13 using tetra-n-butylammonium fluoride was executed in high yield. Attempts at ring-closure of 13 using a variety of oxidants ($VOCl_3$, VOF_3, $Pb(OAc)_4$, $FeCl_3$, TTFA)[10,11] resulted in either recovered starting material or intractable tars. Reaction of protected phenol 12 with non-thallium reagents gave identical results.

Examination of the ^{1}H-NMR spectrum of N-acetylcolchinol ($CDCl_3$ at room temperature) derived both synthetically (from acid 8) and semi-synthetically (from colchiceine)[4b] revealed a 3:1 mixture of conformational isomers. Of particular interest were the doubled resonances corresponding to protons on the acetamide methyl and C-1 methoxyl groups.[16,17] Such atropisomerism has been previously observed in other colchinoids.[2a,18] The biological effects of colchinoids are thought to be mediated through their association with tubulin leading to a substoichiometric inhibition of microtubule assembly. There is evidence which suggests that both colchicine and protein undergo conformational changes when binding occurs.[19] Our synthetic studies have been directed at defining the requisite conformational and fluxional characteristics of the colchicine system necessary for high affinity tubulin association. While the route described above results in racemic material, access to both optical isomers is readily available through enantioselective reduction[20] of intermediate ketone 15. The conformational features of additional colchinoid systems will be reported in due course.

Acknowledgement. We wish to thank Dr. David Reagan for technical assistance and the National Institutes of Health (AM/CA 32453) for support of this research.

REFERENCES

1) Current address: Lilly Research Laboratories, Lilly Corporate Center, Indianapolis, IN 46285

2) For recent reviews of colchicine chemistry and pharmacology and references to background literature, see: a) A. Brossi et al., Med. Res. Rev., 8, 77 (1988); H. G. Capraro, A. Brossi in "The Alkaloids," Vol. XXIII, A. Brossi, Ed., Academic Press, 1984; c) A. Brossi, Trends Pharmocol. Sci., 4, 327 (1983); d) A. G. Gilman, L. S. Goodman, and A. Gilman, Eds., "The Pharmacological Basis of Therapeutics," 7th ed., MacMillan Pub. Co., New York, 1985, pp. 708-710.

3) For recent SAR studies in the modified colchicine series, see: a) F. R. Quinn, J. A. Beisler, J. Med. Chem., 24, 251 (1981); b) F. R. Quinn, Z. Neiman, and J. A. Beisler, J. Med. Chem., 24, 636 (1981); c) M. Rösner, H. G. Caparo, A. E. Jacobson, L. Atwell, A. Brossi, M. A. Iorio, T. H. Williams, R. H. Sir, and C. F. Chignell, J. Med. Chem., 24, 257 (1981); d) A. Brossi, P. N. Sharma, L. Atwell, A. E. Jacobson, M. A. Iorio, R. Molinari, and C. F. Chignell, J. Med. Chem., 26, 1365 (1983).

4) a) A. Windaus, Sitzungsb. Heidelberg. Akad. Wiss., 18 Abh., S.7 (1914); b) J. Cech and F. Šantavý, Coll. Czech. Commun., 532 (1949).

5) M. A. Iorio, Heterocycles, 22, 2207 (1984).

6) For another degradative route from colchiceine see: H. Lettré, H. Fernholz, and E. Hartwig, Ann., 576,147 (1952). See also: H. Fernholz, Ann., 568, 63 (1950).

7) V. V. Kiselev et al., Zh. Org. Chem. (Eng.), 13, 2175 (1977).

8) a) H. Rapoport, A. R. Williams, and M. E. Cisney, J. Am. Chem. Soc., 72, 3324 (1950); b) H. Rapoport, A. R. Williams, and M. E. Cisney, J. Am. Chem. Soc., 73, 1414 (1951).

9) J. W. Cook, J. Chem. Soc., 863 (1951).

10) a) A. McKillop, A. G. Turrell, D. W. Young, and E. C. Taylor, J. Am. Chem. Soc., 102, 6504 (1980); b) E. C. Taylor, A. McKillop et al., J. Am. Chem. Soc., 103, 6856 (1981); c) E. C. Taylor, A. McKillop et al., J. Org. Chem., 46, 3078 (1981); d) E. C. Taylor, J. G. Andrade, G. J. H. Rall, and A. McKillop, J. Am. Chem. Soc., 102, 6513 (1980); e) R. C. Cambie, M. G. Dunlop, P. S. Rutledge, and P. D. Woodgate, Syn. Commun., 10, 827 (1980).

11) a) T. Kametani and K. Fukumoto, Synthesis, 657 (1972); b) T. Kametani et al., J. Am. Chem. Soc., 99, 3805 (1977); c) M. A. Schwartz et al., J. Am. Chem. Soc., 99, 2571 (1977); d) D. A. Whiting and A. F. Wood, Tet. Lett., 2335 (1978); e) S. M. Kupchan, O. P. Dhingra, and C.-K. Kim, J. Org. Chem., 43, 4076 (1978); f) E. McDonald and A. Suksamram, J. Chem. Soc., Perkin I, 440 (1978); g) J. Quick and R. Ramachandra, Tet., 1301 (1980); h) G. E. Schneiders and R. Stevenson, J. Org. Chem., 46, 2969 (1981); i) C. Szantay et al., J. Org. Chem., 47, 594 (1982); j) C. Szantay et al., Heterocycles, 273 (1983).

12) All new compounds have been fully characterized by ^{1}H-NMR (90 MHz, 100 MHz, or 360 MHz), ^{13}C-NMR (22.5 MHz or 90MHz), IR, and mass spectroscopy.

13) Direct displacement of the tosylate obtained from alcohol 10 gave no reaction. Introduction of nitrogen by way of Mitsunobu conditions or reductive amination of the derived ketone 15 likewise met with failure. See also: H. Lettré and H. Fernholz, Z. Physiol. Chem., 278, 175 (1943).

14) For leading references see: a) S. N. Maiti, M. P. Singh, and R. G. Micetich, Tet. Lett., 1423 (1986); b) T. Gartiser, C. Selve, and J.-J. Delpuech, Tet. Lett., 1609 (1983); F. Rolla, J. Org. Chem., 47, 4327 (1982).

15) Synthetic N-acetylcolchinol was identical in all aspects to an authentic sample prepared from colchiceine as described by Šantavý.[4b]

16) 90 MHz ^{1}H-NMR spectrum of N-acetylcolchinol at room temperature ($CDCl_3$, Me_4Si, ∂): 7.51 (d, 1H, J = 9 Hz), 7.0 (m, 2H), 6.71 (d, 1H, J = 9 Hz), 6.57 (s, 1H), 6.01 (bd, 1H, J = 7 Hz), 4.8 (m, 1H), 3.92 (s, 3H), 3.89 (s, 3H), [3.51, 3.59 (s, 3H, C-1 CH_3O-)], 2.35 (m, 2H), [2.32, 2.03 (s, 3H, -NHCOCH_3)], 2.00 (m, 2H).

17) This doubling of ^{1}H-NMR signals in semi-synthetic N-acetylcolchinol has been previously observed (reference 7) and dubiously ascribed to amide rotomers.

18) W. Gaffield, R. E. Lundin, and R. M. Horowitz, J. Chem. Soc., Chem. Commun., 610 (1984).

19) a) H. W. Detrich, R. C. Williams, Jr., T. L. Macdonald, L. Wilson, and J. D. Puett, Biochemistry, 20, 5999 (1981); b) S. Bane, D. Puett, T. L. Macdonald, and R. C. Williams, Jr., J. Biol. Chem., 259, 7391 (1984); c) H. J. C. Yeh, M. Chrzanowska, and A. Brossi, FEBS Lett., 229, 82 (1988).

20) a) R. Noyori, I. Tomino, and Y. Tanimoto, J. Am. Chem. Soc., 101, 3129 (1979); b) R. Noyori, I. Tomino, and M. Nishizawa, J. Am. Chem. Soc., 101, 5843 (1979); c) R. Noyori, Pure and Appl. Chem., 53, 2315 (1981); d) S. Itsuno, K. Ito, A. Hirao, and S. Nakahama, J. Chem. Soc., Chem. Commun., 469 (1983). See also: D. Seebach et al., Helv. Chim. Acta, 64, 2485 (1981).

(Received in USA 18 May 1988)