

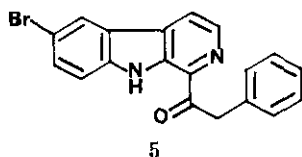
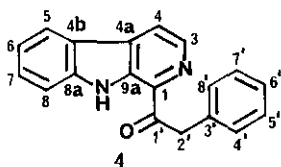
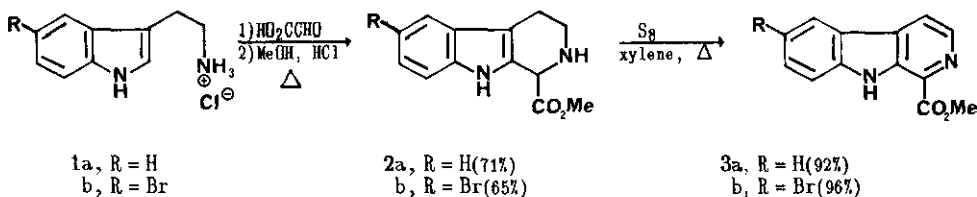
THE SYNTHESIS OF EUDISTOMINS S AND T: β -CARBOLINES FROM THE
TUNICATE EUDISTOMA OLIVACEUM

Ian W.J. Still* and James McNulty

J. Tuzo Wilson Research Laboratories, Erindale Campus, University of Toronto in
Mississauga, Mississauga, Ontario, Canada L5L 1C6

Abstract – The syntheses of two β -carbolines, eudistomins S and T,
have been accomplished from tryptamine precursors.

Since the first reported activity against Herpes simplex virus, type 1 (HSV-1), by the tunicate (ascidian) organism Eudistoma olivaceum,¹ and the subsequent characterization and structural elucidation of fifteen components of the organism by Rinehart *et al.*,^{2,3} in 1984, there has been widespread interest in the structure⁴ and synthesis⁵ of these antiviral β -carboline derivatives, collectively referred to as eudistomins, as well as closely related compounds such as eudistomidin-A.⁶ Recently, the identification of three new members of the eudistomin series, eudistomins R, S, and T, was reported by Kinzer and Cardellina.⁷ We now wish to report the total synthesis of eudistomin T (C₁₉H₁₄N₂O)⁴ and one of its closely related bromo-analogues, eudistomin S (C₁₉H₁₃BrN₂O)⁵.



The starting materials for the synthesis of eudistomins T and S, outlined above, were tryptamine and 5-bromotryptamine,⁸ respectively. Pictet-Spengler condensation of the tryptamine with glyoxylic acid⁹ produced, after esterification, the tetrahydro- β -carbolines (2a,b). Dehydrogenation to the β -carboline system could not be effected with palladium in the presence of the bromo-substituent and we have found elemental sulfur in refluxing xylene¹⁰ to be the reagent of choice for this transformation. The final step was achieved in each case by a modified Grignard reaction¹¹ on the esters 3a,b, providing 4 and 5, in isolated yields of 59% and 40% respectively. Only minor amounts of tertiary alcohol are formed under our

conditions. The use of alkyllithiums for the generation of hydroxy-ketones from γ -lactones has been reported¹² and lithium salts have been reported recently to assist the reaction of organomanganese bromide reagents with acid chlorides and anhydrides.¹³ The role of the lithium salts in the conversion of 3a, b \rightarrow 4 and 5 above is clearly crucial, but as yet unexplained. We are presently exploring the generality of this simple ester to ketone interconversion.

Eudistomins S and T prepared in this way¹⁴ were identical in all respects (ir, uv, ¹H nmr, and mass spectral fragmentation pattern) with the data reported by Kinzer and Cardellina.^{7,15} The synthetic route described here is direct, efficient and appears quite capable of extension to the synthesis of eudistomin R and other potentially interesting analogues of this class of compound.

REFERENCES

1. K.L. Rinehart, Jr., P.D. Shaw, L.S. Shield, J.B. Gloer, G.C. Harbour, M.E.S. Koker, D. Samain, R.E. Schwartz, A.A. Tymiak, D.L. Weller, G.T. Carter, M.H.G. Munro, R.G. Hughes, Jr., H.E. Renis, E.B. Swynenberg, D.A. Stringfellow, J.J. Vavra, J.H. Coats, G.E. Zurenko, S.L. Kuentzel, L.H. Li, G.J. Bakus, R.C. Brusca, L.L. Craft, D.N. Young, and J.L. Connor, Pure Appl. Chem., 1981, **53**, 795.
2. K.L. Rinehart, Jr., J. Kobayashi, G.C. Harbour, R.G. Hughes, Jr., S.A. Mizesak, and T.A. Scahill, J. Am. Chem. Soc., 1984, **106**, 1524.
3. J. Kobayashi, G.C. Harbour, J. Gilmore, and K.L. Rinehart, Jr., J. Am. Chem. Soc., 1984, **106**, 1526.
4. a) J.W. Blunt, R.J. Lake, M.H.G. Munro, and T. Toyokuni, Tetrahedron Lett., 1987, **28**, 1825; b) R.J. Lake, M.M. Brennan, J.W. Blunt, M.H.G. Munro, and L.K. Pannell, Tetrahedron Lett., 1988, **29**, 2255; c) R.J. Lake, J.D. McCombs, J.W. Blunt, M.H.G. Munro, and W.T. Robinson, Tetrahedron Lett., 1988, **29**, 4971.
5. a) S.-Y. Han, M.V. Lakshmikantham, and M.P. Cava, Heterocycles, 1985, **23**, 1671; b) R. Plate, R.H.M. van Hout, H. Behm, and H.C.J. Ottenheijm, J. Org. Chem., 1987, **52**, 555; c) K.L. Rinehart, Jr., J. Kobayashi, G.C. Harbour, J. Gilmore, M. Mascal, T.G. Holt, L.S. Shield, and F. Lafargue, J. Am. Chem. Soc., 1987, **109**, 3378; d) I.W.J. Still and J.R. Strautmanis, Tetrahedron Lett., 1989, **30**, 1041; e) M. Nakagawa, J.-J. Liu, and T. Hino, J. Am. Chem. Soc., 1989, **111**, 2721.
6. Y. Murakami, H. Takahashi, Y. Nakazawa, M. Koshimizu, T. Watanabe, and Y. Yokoyama, Tetrahedron Lett., 1989, **30**, 2099.
7. K.F. Kinzer and J.H. Cardellina II, Tetrahedron Lett., 1987, **28**, 925.
8. a) B.T. Ho, W.M. McIsaac, and L.W. Tansey, J. Pharm. Sci., 1969, **58**, 563; b) G.F. Smith, J. Chem. Soc., 1954, 3842.
9. B.T. Ho and K.E. Walker, Org. Synth., 1971, **51**, 136.
10. H.R. Snyder, C.H. Hansch, L. Katz, S.M. Parmeter, and E.C. Spaeth, J. Am. Chem. Soc., 1948, **70**, 219.

11. Benzylmagnesium chloride (2.05 equiv.), LiCl (8.0 equiv.), in refluxing diethyl ether, 25 min.
12. S. Cavicchioli, D. Savoia, C. Trombini, and A. Umami-Ronchi, *J. Org. Chem.*, 1984, **49**, 1246 .
13. G. Cahiez and B. Laboue, *Tetrahedron Lett.*, 1989, **30**, 3545 .
14. Both eudistomins have been obtained as (yellow) crystalline compounds for the first time; eudistomin T(4), mp 160–161°C (MeOH) and eudistomin S(5), mp 168°C (MeOH).
15. ¹³C Nmr data, (below) are recorded for 4 and 5 (Varian XL 400, 21°C); (4) $\delta(\text{CDCl}_3)$: 43.8(C-2'), 111.8(C-8), 119.1(C-4), 120.4(C-4b), 120.6(C-6), 121.7(C-5), 126.7(C-6'), 128.4(C-5', C-7'), 129.1(C-7), 130.0(C-4', C-8'), 131.4(C-4a), 135.0, 135.2, 135.8(C-3', C-8a, C-9a), 138.1(C-3), 140.9(C-1), 202.1(C-1'); (5) $\delta(\text{CDCl}_3)$: 43.8(C-2'), 113.3(C-8), 113.5(C-6), 119.2(C-4), 122.3(C-4b), 124.5(C-5), 126.8(C-6'), 128.5(C-5', C-7'), 130.0((C-4', C-8'), 130.4(C-4a), 132.0(C-7), 134.8, 135.6, 136.0(C-3', C-8a, C-9a), 138.5(C-3), 139.5(C-1), 202.2(C-1').

Received, 17th July, 1989