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SYNTHESIS OF N(10)-ACETYLEUDISTOMIN L

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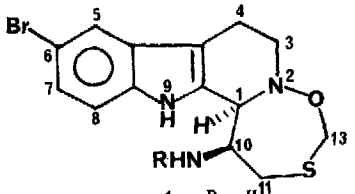
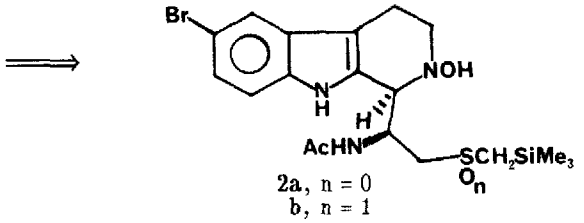
Summary: The marine indole alkaloid derivative N(10)-acetyleudistomin L has been prepared in a convergent synthesis, starting from 5-bromoindole and L-cysteine.

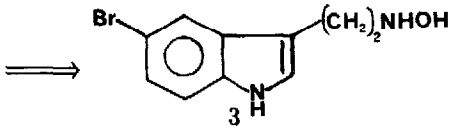
In 1984 Rinehart and coworkers reported the structure determination of 15 indole alkaloids, named the eudistomins, which they had isolated from the tunicate Eudistoma olivaceum.[1] Reports of additional eudistomins and the related eudistomidin-A have since appeared.[2-5] The eudistomins C, E, K and L contain the novel 1,3,7-oxathiazepine ring and demonstrate strong antiviral activity. During the course of our work on the synthesis of eudistomin L **1a**, several reports[6-8] have appeared describing efforts towards the synthesis of these compounds. Herein we report the synthesis of N(10)-acetyleudistomin L **1b**.



1a, R = H[11]
b, R = Ac



2a, n = 0
b, n = 1



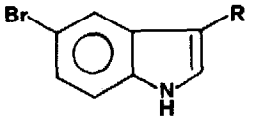
3

OHCCH(NHAc)$CH_2SCH_2SiMe_3$

4

We planned to sequentially build ring C on to the indole ring system, followed by ring D, utilizing the elements of the amino acid L-cysteine as shown in the retrosynthetic scheme above. The hydroxylamine **3** was prepared in four steps starting from 5-bromoindole,[9] via the known aldehyde **5a** ($POCl_3$(1.35eq)/DMF, 95%)[10] and nitroolefin **5b** (NH_4OAc(0.3eq)/CH_3NO_2/100°C/2.5h, 70%).[11] Reduction of **5b** ($NaBH_4$(1.5eq)/THF:CH_3OH=9:1/23°C/1h), according to a procedure by Varma and Kabalka for nitrostyrenes,[12] gave the corresponding saturated nitro compound **5c** in 80% yield after flash chromatography on silica gel (R_f=0.50, CH_2Cl_2) and recrystallization (mp 91-92.5°C, $CHCl_3$/hexanes).[13] Further reduction (Zn°(6.5eq)/NH_4Cl(2.0eq)/THF:H_2O=2:1/ 23°C/2.5h),

according to a procedure described by Corey and Estreicher,[14] gave **3** in yields of 80–85%. Compound **3** was readily distinguished by ^{1}H NMR (NHOH, 2H, δ = 5.5ppm ($CDCl_3$)) from the related 5-bromotryptamine (NH_2, 2H, δ = 1.8ppm ($CDCl_3$)), prepared by more vigorous reduction ($LiAlH_4$/THF) of **5b**.



$MeO_2CCH(NHR')CH_2SR''$

5a R = CHO
5b R = CH = $CHNO_2$
5c R = $CH_2CH_2NO_2$

6a R' = H, R'' = H
6b R' = H, R'' = $CH_2Si(CH_3)_3$
6c R' = $COCH_3$, R'' = $CH_2Si(CH_3)_3$

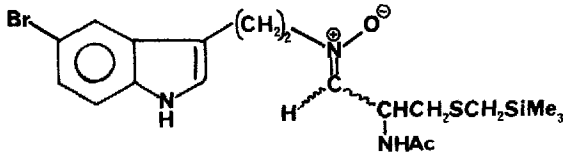
The aldehyde **4** could be prepared in five steps starting from L-cysteine, via its methyl ester hydrochloride (CH_3OH/HCl(g)/25°C/24h, 65%).[15] The liberated free base **6a** ($NaHCO_3/H_2O/CH_2Cl_2$, 85%) was S-alkylated ($ClCH_2Si(CH_3)_3$(1.3eq)/K_2CO_3 (2.0eq)/DMF/25°C/16h) to give the unstable α-amino ester **6b** in 75% yield (bp 120–125°C/0.2 torr; $[\alpha]_D^{23}$ = +16.5° (c 7.0, CH_2Cl_2)). This was immediately acylated (Ac_2O(1.8 eq)/NEt_3(5.0eq)/CH_2Cl_2/25°C/20h) to give **6c** in 95% yield (bp 180–190°C/0.2 torr; $[\alpha]_D^{23}$ +35.0° (c 5.0, toluene)).[13] Reduction of **6c** (DIBAL(2.5eq)/toluene/–60°C/2.5h) was problematic and despite various changes to the reaction conditions we have been able to obtain the aldehyde **4**, as contained in silica gel chromatographic fractions (R_f=0.30, CH_2Cl_2:EtOAc = 1:1) enriched in the substance, in only 40–50% yields. In practice, however, we were able to use the crude aldehyde in the subsequent steps without recourse to any further purification.

Ring C was formed in a two-step process. Initial condensation of hydroxylamine **3** and aldehyde **4** ($MgSO_4$(10.0eq)/CH_2Cl_2/0–5°C(7h), 25°C(1h)) gave the crude nitrone **7** as a fluffy yellow solid to which was immediately applied a modification of the Pictet-Spengler reaction (CF_3CO_2H (3.0eq)/CH_2Cl_2/25°C/16h) to give the cyclized compound **2a**[13] as a beige solid (mp 214–216°C, EtOAc). In a typical operation, hydroxylamine **3**, derived from the saturated nitro compound **5c** (2.05 g, 7.62 mmol) and reacted with crude aldehyde **4** derived from the protected ester **6c** (3.20 g, 12.1 mmol), yielded 0.86 g (1.83 mmol) of the ring C cyclized compound **2a** in 24% recrystallized yield, based on the saturated nitro compound **5c**.

Compound **2a** was racemic, with racemization likely a result of α-deprotonation of the O-protonated nitrone **7** during the modified Pictet-Spengler reaction to give the corresponding N-hydroxyenamine. Compound **2a**, however, was a single diastereomer based on its 400MHz ^{1}H NMR

spectrum and possessed the correct relative stereochemistry, as shown by the spectral analysis of later products in the synthesis.

Closure of ring D to give N(10)-acetyleudistomin L **1b** as shown, was carried out by a sila-Pummerer reaction [16] of the diastereomeric mixture of sulfoxides **2b**, obtained in 70% yield from **2a** (m-CPBA(1.25eq)/$NaHCO_3$(4.0eq)/THF/0-5°C/2.5h; reprecipitated from CH_2Cl_2).



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2b $\xrightarrow[23° \longrightarrow 80°C\ (0.5h)\ 80°C\ (1h)]{0.02\ M\ in\ CH_3CN}$ **1b**

Compound **1b** was obtained in 17-21% yield as a white solid (mp 193.5-195.5°C) after column chromatography on deactivated neutral alumina (R_f=0.70, CH_2Cl_2:CH_3OH = 98:2). No side products have as yet been identified. The spectroscopic data[17] for **1b** are in very close agreement with those reported for the closely related O(6), N(10)-bisacetyl derivative of eudistomin C[1a] and the N(10)-acetyl derivative[5a] of eudistomin K.

We have been unable to remove the N-acetyl group under a variety of conditions employing reagents such as KOH, LiOH, $NaOCH_3$, NH_2NH_2, or HCl. Interestingly, 0.5M HCl in THF:H_2O = 3:1 did not decompose **1b** even at 50°C, perhaps indicating internal protection of the O,S - acetal functionality by adjacent N-protonation. Further work on improving this aspect of our synthesis and on the development of an enantiospecific route to eudistomin L **1a** and its congeners is in progress.

Acknowledgement

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References

1. a) K.L. Rinehart Jr., J. Kobayashi, G.C. Harbour, R.G. Hughes Jr., S.A. Mizsak, and T.A. Scahill. *J. Am. Chem. Soc.* **1984**, *106*, 1524.
   b) J. Kobayashi, G.C. Harbour, J. Gilmore, and K.L. Rinehart Jr. *J.Am.Chem.Soc.* **1984**, *106*, 1526.
2. J. Kobayashi, H. Nakamura, Y. Ohizumi, and Y. Hirata. *Tetrahedron Lett.* **1986**, *27*, 1191.

3. 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.
4. K.F. Kinzer and J.H. Cardellina II. *Tetrahedron Lett.* **1987**, *28*, 925.
5. a) R.J. Lake, M.M. Brennan, J.W. Blunt, M.H.G. Munro, and L.K. Pannell. *Tetrahedron Lett.* **1988**, *29*, 2255.
   b) R.J. Lake, J.D. McCombs, J.W. Blunt, M.H.G. Munro, and W.T. Robinson. *Tetrahedron Lett.* **1988**, *29*, 4971.
6. S.-Y. Han, M.V. Lakshmikantham and M.P. Cava. *Heterocycles* **1985**, *23*, 1671.
7. R. Plate, R.H.M. van Hout, H. Behm, and H.C.J. Ottenheijm. *J.Org.Chem.* **1987**, *52*, 555.
8. M. Nakagawa, J. Liu, K. Ogata, and T. Hino. *J.Chem.Soc., Chem.Commun.* **1988**, 463.
9. a) J. Thesing, G. Semler and G.Mohr. *Chem.Ber.* **1962**, *95*, 2205.
   b) 5-Bromoindole is available commercially from the Aldrich Chemical Company.
10. a) G. Cavallini and V. Ravenna. *Il Farmaco (Pavia) Ed.Sci.* **1958**, *13*, 105; *Chem.Abstr.* 1958, *52*, 20126.
    b) G.F. Smith. *J.Chem.Soc.* **1954**, 3842.
11. a) B.T. Ho, W.M. McIsaac and L.W. Tansey. *J.Pharm.Sci.* **1969**, *58*, 563.
    b) E.H.P. Young. *J.Chem.Soc.* **1958**, 3493.
12. R.S. Varma and G.W. Kabalka. *Synth.Commun.* **1985**, *15*, 151.
13. All new compounds provided IR, ^{1}H NMR and MS data and elemental analysis results in accord with their proposed structures.
14. E.J. Corey and H. Estreicher. *J.Am.Chem.Soc.* **1978**, *100*, 6294.
15. a)M. Bergmann and G. Michalis. *Chem.Ber.* **1930**, *63*, 987.
    b) L. Zervas and I. Photaki. *J.Am.Chem.Soc.* **1962**, *84*, 3887.
16. A.G. Brook and D.G. Anderson. *Can.J.Chem.* **1968**, *46*, 2115.
17. Compound **1b**: IR, ^{1}H and ^{13}C NMR, MS and HR MS data are listed below:
    IR (KBr) 3410(s), 3229(m), 3100(w), 2920(m), 2847(m), 1653(s), 1510(s), 1446(w), 1309(m), 1041(m) and 793(m) cm^{-1}; ^{1}H NMR(400MHz),($CDCl_3$) δ8.93 (br s, N(9)-H), 7.53(s, H_5), 7.17(dd, J=8.6,1.8Hz, H_7), 7.12(d, J=8.6Hz, H_8), 6.59(d, J=9.9Hz, N(10)-H), 5.00(m, H_{10}), 4.94(d, J=9.0Hz, H_{13}), 4.80(d, J=9.0Hz, H_{13}), 4.13(br s, H_1), 3.58(m, H_3), 3.30(d, J=14.6Hz, H_{11}), 3.11(td, J=11.0,4.3Hz, H_3), 2.88(m, H_4), 2.76(m, H_4, H_{11}) and 1.73(s, CH_3) ppm; ^{13}C NMR(100MHz),($CDCl_3$) δ170.3 (C=O), 135.7(C_{8a}), 131.8(C_{9a}), 127.9(C_{4b}), 124.6(C_7), 120.6(C_5), 113.0(C_8), 112.6(C_6), 108.8(C_{4a}), 71.0(C_{13}), 68.9(C_1), 54.8(C_3), 46.9(C_{10}), 32.1(C_{11}), 23.2(CH_3), 20.5(C_4) ppm; MS(EI) m/z(%) 397(17), 195(17), 312(24), 310(24), 282(15), 280(17), 267(23), 266(99), 265(25), 264(100), 250(13), 249(26), 248(15), 247(25), 186(11), 185(17), 168(24); HR MS observed: 395.03030, calcd. for $C_{16}H_{18}{}^{79}BrN_3O_2S$: 395.03012.

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