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A Concise Synthesis of Two Pyrroles of Marine Origin

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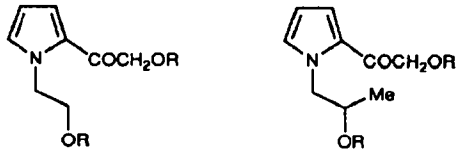
Abstract. 2-Ethanolamine and (2R)-2-aminopropanol were converted into their N-pyrrole derivatives, 14 and 15, by reaction with 2,5-dimethoxytetrahydrofuran. The acetoxyacetyl derivatives of 14 and 15 were prepared and submitted to BBr_3-promoted rearrangement. Acetylation of the resulting (2-acetoxyacetyl)pyrrol-1-yl-2-ethanol and 2-propanol furnished the corresponding acetates.

Pyrroles are rarely found in the marine environment and are usually confined to sponges,[1] bryozoans,[2] cyanobacteria and brown algae.[3] Recently, two simple, yet novel, 2-acylated pyrroles were isolated in extremely small amounts from samples of *Gracilariopsis lemaneiformis*, a red alga which flourishes in intertidal pools on the coast of Oregon, USA, at Cape Perpetua.[4] As the extraction procedure entailed treatment with acetic anhydride, it was not known whether the natural products were alcohols (**1** and **3**) or the corresponding acetates (**2** and **4**). In addition, the configurations of **3** and **4** were equally unknown. It was therefore desirable to procure these scarce substances in tangible quantities and confirm their structures.

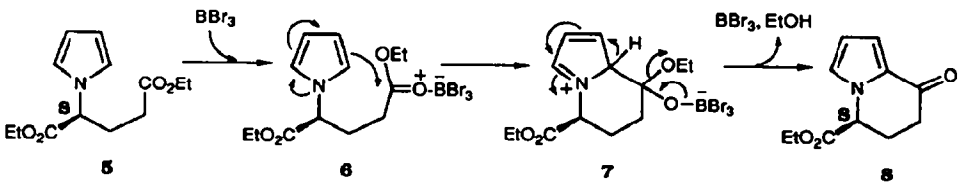


1 R = H
2 R = COMe

3 R = H
4 R = COMe

We now describe a practical synthesis of **2** and **4** which is based on our recently discovered method for effecting the intramolecular acylation of certain N-substituted pyrroles.[5] Typically, the treatment of the N-pyrrole derivative of diethyl L-glutamate (**5**) with 1.1 equivalents of boron tribromide for 15 minutes brings about cyclization to the keto ester **8** in high yield and with total retention of configuration[5] (Scheme 1).

Scheme 1

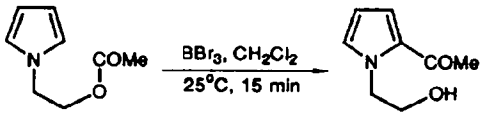


5 **6** **7** **8**

Although the precise mechanism is open to conjecture, the ester group is undoubtedly activated by complexation (**5**→**6**) thereby triggering attack by the pyrrole ring at the α position (**6**→**7**) with excision, at least formally, of a molecule of ethanol (**7**→**8**). In the meantime, the other ester group remains unaffected. An obvious corollary would be the intramolecular detachment of the acyl component of a pendent acetate sub-

stituent. Indeed, exposure of 2-(1H-pyrrol-1-yl)ethyl acetate (**9**) to boron tribromide gave 2-acetylpyrrol-1-yl-2-ethanol (**10**) in high yield[6] (Scheme 2). Clearly, the six-membered transition structure proposed above is propitious for acyl transfer.[7,8]

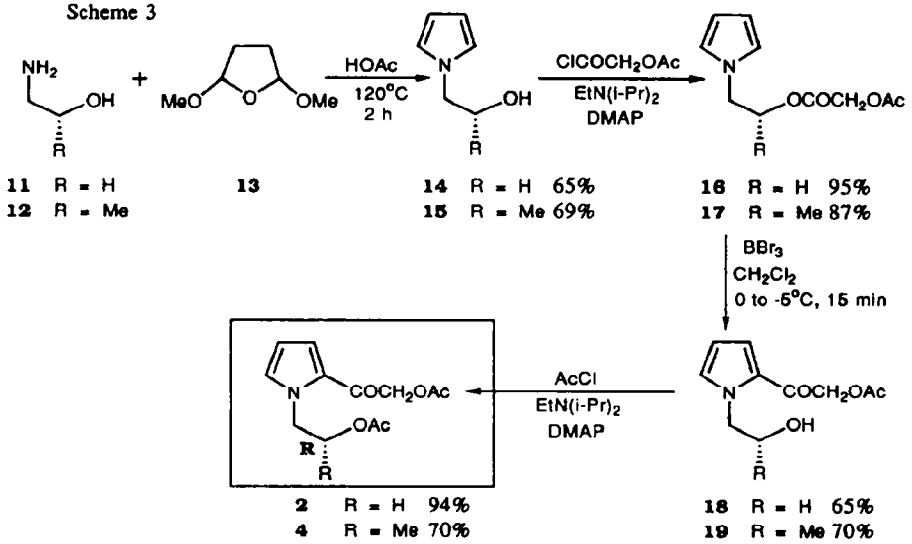
Scheme 2



9 **10** 83%

Having thus established the validity of the key synthetic step the appropriately substituted precursors needed to be assembled. The condensation of 2-ethanolamine (**11**) and (2R)-2-aminopropanol (**12**) with 2,5-dimethoxytetrahydrofuran (**13**) in hot acetic acid provided the N-pyrrole alcohols **14** and **15** in yields of 65 and 69% respectively[9] (Scheme 3). Next, esterification of **14** and **15** was effected with acetoxyacetyl chloride in the presence of an equivalent of N-ethyldiisopropylamine and a catalytic amount of 4-dimethylaminopyridine (DMAP) in methylene chloride. Reaction was rapid giving high yields of the desired precursors,[10] the acetoxyacetates **16** and **17**. Gratifyingly, the crucial intramolecular acylation step proceeded efficiently.[11] Submission of **16** and **17** to boron tribromide (1.1 equivalents) at 0° to -5°C in dichloromethane for 15 minutes furnished exclusively the two acetoxyacetylpyrrole alcohols (**18** and **19**). Contrary to expectation, no bromination of the newly liberated hydroxyl group occurred, although alcohols, particularly secondary and tertiary ones, are usually converted to the corresponding bromides under these conditions.[12] Finally, treatment of **18** and **19** with acetyl chloride and N-ethyldiisopropylamine and a catalytic amount of DMAP in methylene chloride afforded the target molecules **2** and **4** in yields of 94 and 70% respectively.

Scheme 3



11 R = H
12 R = Me

13

14 R = H 65%
15 R = Me 69%

16 R = H 95%
17 R = Me 87%

2 R = H 94%
4 R = Me 70%

18 R = H 65%
19 R = Me 70%

These synthetic samples[13,14] exhibited ^{1}H- and ^{13}C-NMR spectra which were entirely compatible with those reported[4] for the naturally occurring products. However, the value of $[\alpha]_D^{20}$ -47.2° (c 0.29, MeOH) recorded for **4** of natural origin is considerably lower than that observed for the synthetic material. This discrepancy is probably due to partial racemization which occurred in the methanolic solution during measurement or, more likely, in the aqueous methanol used as eluent for the final stage of chromatographic purification. Nevertheless, the negative rotations seen in both cases indicate that the natural sample **4** must have the R configuration.

In conclusion, the pyrrole acetates **2** and **4** were obtained in just four steps from the readily available amino alcohols in overall yields of 38 and 30% respectively. At the same time, a new procedure of BBr_3-promoted intramolecular and regioselective acylation of pyrroles has been developed which should find further application.

Acknowledgment. We thank the Swiss National Science Foundation for support of this work (grant # 20-32'166.91).

References and Notes

1. M. Aknin, J. Miralles, J.M. Kornprobst, R. Faure, E.M. Gaydou, N. Boury-Esnault, Y. Kato, J. Clardy, *Tetrahedron Lett.* **1990**, *31*, 2979.
2. B. Carté, D.J. Faulkner, *J. Org. Chem.* **1983**, *48*, 2314.
3. C. Christopherson in "*The Alkaloids*" (Ed. A. Brossi), Academic Press, Orlando, FL, 1985, Vol. XXIV, pp. 25-111.
4. Extraction of 1.2 kg of alga (dry weight) gave, after work-up, 2 mg and 2.9 mg of **2** and **4** respectively (Z.D. Jiang, W.H. Gerwick, *J. Nat. Prod.* **1991**, *54*, 403).
5. C.W. Jefford, S.R. Thornton, K. Sienkiewicz, *Tetrahedron Lett.* **1994**, *35*, 3905.
6. Acetate **9** was prepared by condensing 2-ethanolamine with 2,5-dimethoxytetrahydrofuran (see ref. 9) and treating the product so obtained with acetyl chloride, N-ethyl diisopropylamine (1 equivalent each) and 5% DMAP in CH_2Cl_2. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 2.06 (s, 3H), 4.09-4.15 (m, 2H), 4.28-4.34 (m, 2H), 6.16 (t, J = 2.1 Hz, 2H), 6.68 (t, J = 2.1 Hz, 2H). Alcohol **10** was purified by flash chromatography (SiO_2, Et_2O). IR (neat): 3404, 1649. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 2.45 (s, 3H; brs, 1H), 3.91 (t, J = 5.1 Hz, 2H), 4.48 (t, J = 5.1 Hz, 2H), 6.17 (dd, J = 4.0, 1.5 Hz, 1H), 6.94 (t, J = 2.0 Hz, 1H), 7.01 (dd, J = 4.0, 1.5 Hz, 1H).
7. Despite precedent, namely the reaction of BBr_3 with lactones to give ω-bromoacyloxyborane intermediates, there was no evidence in the present instance for the formation of bromides (G.A. Olah, R. Karpeles, S.C. Narang, *Synthesis* **1982**, 963).
8. It is well to remember that N-substituted pyrroles usually undergo preponderant 3-acylation under the Vilsmeier-Haack conditions (J.M. Muchowski in "Advances in Medicinal Chemistry", Eds. B.E. Maryanoff and C.A. Maryanoff, vol. 1, JAI Press, Greenwich, CT, USA, 1992, p. 117; C.W. Jefford, Q. Tang, J. Boukouvalas, *Tetrahedron Lett.* **1990**, *31*, 995). A related example of intramolecular 2-acylation is the $AlCl_3$-catalyzed rearrangement of the mixed anhydride of an N-substituted pyrrolylacetic acid (C.W. Jefford, Q. Tang, A. Zaslona, *J. Am. Chem. Soc.* **1991**, *113*, 3513).

9. The literature procedure was followed except that the crude pyrrole alcohols **14** and **15** (yields 80 and 89% respectively) were purified by bulb-to-bulb distillation at 110-115°C/12 Torr (H. Carpio, E. Galeazzi, R. Greenhouse, A. Guzmán, E. Velarde, Y. Antonio, F. Franco, A. Leon, V. Pérez, R. Salas, D. Valdés, J. Ackrell, D. Cho, P. Gallegra, O. Halpern, R. Koehler, M.L. Maddox, J.M. Muchowski, A. Prince, D. Tegg, T.C. Thurber, A.R. Van Horn, D. Wren, *Canad. J. Chem.* **1982**, *60*, 2295). **15** had $[\alpha]_D^{20}$ -25.3° (c 1.56, MeOH). ^{1}H-NMR (200 MHz, $CDCl_3$): **14**, δ 1.72 (s, 1H), 3.81-3.84 (m, 2H), 3.99-4.02 (m, 2H), 6.17 (t, *J* = 2.2 Hz, 2H), 6.70 (t, *J* = 2.2 Hz, 2H); **15**, δ 1.21 (d, *J* = 6.3 Hz, 3H), 1.70 (s, 1H), 3.74 (ABX dd, *J* = 14.0, 8.1 Hz, 1H), 3.93 (ABX dd, *J* = 14.0, 3.3 Hz, 1H), 4.00-4.07 (m, 1H), 6.17 (t, *J* = 2.2 Hz, 2H), 6.68 (t, *J* = 2.2 Hz, 2H).

10. Acetoxyacetyl chloride, purchased from *Aldrich Chemie*, CH-9470 Buchs, reacted equally quickly with the primary and secondary alcohols **14** and **15**. The resulting acetoxyacetates, **16** and **17**, were obtained as colorless oils after flash chromatography (SiO_2, Et_2O:hexane, 2:1). **17** had $[\alpha]_D^{20}$ +11.6° (c 0.99, $CHCl_3$). ^{1}H-NMR (200 MHz, $CDCl_3$): **16**, δ 2.16 (s, 3H), 4.15 (t, *J* = 5.5 Hz, 2H), 4.41 (t, *J* = 5.5 Hz, 2H), 4.60 (s, 2H), 6.17 (t, *J* = 2.2 Hz, 2H), 6.67 (t, *J* = 2.2 Hz, 2H); **17**, δ 1.22 (d, *J* = 6.3 Hz, 3H), 2.16 (s, 3H), 3.95-4.04 (m, 2H), 4.57 (AB m, *J* = 15.8 Hz, 2H), 5.16-5.24 (m, 1H), 6.15 (t, *J* = 2.2 Hz, 2H), 6.63 (t, *J* = 2.2 Hz, 2H).

11. The procedure has been described previously (ref. 5). Flash chromatography (SiO_2, Et_2O) yielded pure **18** and **19** as a white solid (m.p. 38-40°C) and a colorless viscous oil ($[\alpha]_D^{20}$ -70.2° (c 1.01, $CHCl_3$)), respectively. ^{1}H-NMR (400 MHz, $CDCl_3$): **18**, δ 2.00 (brs, 1H), 2.21 (s, 3H), 3.89 (t, *J* = 5.2 Hz, 2H), 4.46 (t, *J* = 5.2 Hz, 2H), 5.14 (s, 2H), 6.20 (dd, *J* = 4.0, 3.0 Hz, 1H), 7.01-7.03 (m, 2H); **19**, δ 1.23 (d, *J* = 5.9 Hz, 3H), 2.21 (s, 3H and brs, 1H), 4.02-4.12 (m, 2H), 4.54 (ABX dd, *J* = 12.9, 2.2 Hz, 1H), 5.15 (s, 2H), 6.21 (dd, *J* = 4.0, 2.2 Hz, 1H), 7.00 (t, *J* = 2.0 Hz, 1H), 7.03 (dd, *J* = 4.0, 1.5 Hz, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$): **18**, δ 20.50, 51.74, 62.61, 65.25, 108.92, 119.54, 126.81, 132.16, 170.51, 182.94; **19**, δ 20.57, 20.62, 56.50, 65.31, 67.83, 108.99, 119.61, 127.09, 132.30, 170.53, 183.17.

12. J.D. Pelletier, D. Poirier, *Tetrahedron Lett.* **1994**, *35*, 1051.

13. Synthetic samples **2** and **4** as well as the new compounds **14-19**, gave acceptable elemental analyses.

14. Acetates **2** and **4** were purified by flash chromatography (SiO_2, Et_2O:hexane, 2:1) and obtained as colorless oils. **2**, IR (neat): 1746, 1668. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 2.01 (s, 3H), 2.21 (s, 3H), 4.35 (t, *J* = 5.2 Hz, 2H), 4.57 (t, *J* = 5.2 Hz, 2H), 6.19 (dd, *J* = 4.0, 2.6 Hz, 1H), 6.92 (t, *J* = 1.9 Hz, 1H), 7.01 (dd, *J* = 4.4, 1.5 Hz, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 20.59, 20.72, 48.43, 63.69, 65.25, 109.02, 119.44, 126.83, 131.62, 170.48, 170.58, 182.72. **4**, $[\alpha]_D^{20}$ -110.6 (c 1.13, MeOH); this value drifted downwards ~3.5° over 10 mins. $[\alpha]_D^{20}$ -103.1° (c 0.80, $CHCl_3$) (value invariant with time). IR (neat): 1741, 1667. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.25 (d, *J* = 6.6 Hz, 3H), 1.94 (s, 3H), 2.21 (s, 3H), 4.15 (ABX dd, *J* = 14.0, 8.5 Hz, 1H), 4.74 (ABX dd, *J* = 14.0, 2.9 Hz, 1H), 5.07 (AB d, *J* = 15.8 Hz, 1H), 5.14-5.22 (m, 1H), 5.21 (AB d, *J* = 15.8 Hz, 1H), 6.16 (dd, *J* = 4.0, 2.6 Hz, 1H), 6.90 (t, *J* = 2.0 Hz, 1H), 6.98 (dd, *J* = 4.0, 1.5 Hz, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 17.35, 20.61, 20.98, 53.42, 65.25, 70.22, 108.85, 119.30, 127.06, 131.59, 169.95, 170.48, 182.80.

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