A practical regiospecific approach towards acronycine and related alkaloids

R.C. Anand* and N. Selvapalam

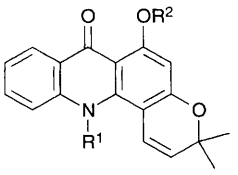
Department of Chemistry, Indian Institute of Technology, Hauz Khas, New Delhi-110 016, India

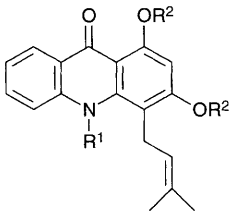
Highly regiospecific prenylation of 3,5-dimethoxyacetanilide and cyclization of 2-[3,5-dimethoxy-2-(3-methylbut-2-enyl)]aminobenzoic acid 6 under mild conditions in high yields provides a practical and flexible synthesis of acronycine, glycocitrine-II and des-*N*-methylacronycine.

Prenylated acridone alkaloids have been isolated from a variety of plant sources and exhibit a broad spectrum of biological activities.[1] Acronycine in particular has attracted attention because it has demonstrated antineoplastic activity against a wide range of experimental neoplasm including C-1498 myelogenous leukemia, a tumour which is singularly non-responsive to other antitumour agents.[2] In view of the biological activity of this natural product, many synthetic investigations[3,4] have been carried out on acronycine and its analogues.[5,6] However, to the syntheses recorded either have circuitous routes resulting in poor overall† yields or afford a mixture of angular and linear isomers.

Here we wish to report our observations which have led to a highly regiospecific synthesis of acronycine **1**, glycocitrine-II **4** and des-*N*-methylacronycine **2** in 60, 64 and 59% overall yields respectively. The present approach, in addition to being a practical route, can be utilized for the synthesis of a number of analogues with modified ring A (through any β-keto-ester), angular pyran ring (*via* cleavage of prenyl group) and variations in the substituents at the N and O atoms of **1**. Another feature of the present pathway is the possible entry into regioselective synthesis of naturally occurring prenylated coumarins[7] (potentially biologically important compounds) through the intermediate 3,5-dimethoxy-2-(3-methylbut-2-enyl)acetanilide **5**.‡

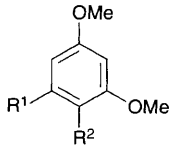
The present synthetic approach is based on our observation that when a mixture of commercially available 3,5-dimethoxyacetanilide, 3-methyl-but-1-en-3-ol and a catalytic amount of $BF_3{\cdot}Et_2O$ was refluxed in dioxane,a yield of 89–92% 2-prenylated acetanilide§ **5** was obtained (mp 104–105 °C) with trace amount (5–6%) of 2,6-diprenylated acetanilide which could be conveniently separated by SiO_2 column chromatography. No 4-substituted-3,5-dimethoxyacetanilide or demethoxylated product could be detected (^{1}H NMR, ^{13}C NMR, TLC). Alkaline hydrolysis of **5** and condensation of the corresponding, crude aniline with diphenyliodinium-2-carboxylate[8] in $(CH_3)_2CHOH$ in the presence of $Cu(OAc)_2$ furnished *N*-substituted anthranilic acid§ **6** in 92–94% yield (mp 133–134 °C). Cyclization of **6** was attempted with $POCl_3$, CF_3CO_2H, $(CF_3CO)_2O$ and PPE under literature reported[1,4] conditions but the yield of the dimethyl ether of *nor*glycocitrine-II **3** was very poor (0–18%) because the prenyl group does not survive under the reaction conditions. However, the reaction of *N*-substituted anthranilic acid **6** with PPE under rigorously anhydrous conditions followed by quenching of the reaction mixture through slow addition to cold $NaHCO_3$ solution, gave an 88–91% yield of **3** after column chromatography on SiO_2. The transformation of this intermediate **3** into glycocitrine-II **4** was carried out by *N*-methylation of **3** with MeI followed by demethoxylation of the resulting crude product with EtSNa–DMF. Acronycine **1** was obtained from **3** by demethoxylation with EtSNa–DMF followed by cyclization of the resulting **3a**§ with DDQ in *o*-$Cl_2C_6H_4$ and then methylation[2] of **2a** with excess of MeI. Des-*N*-methylacronycine **2** was procured from **2a** by selective *O*-methylation with CH_2N_2–$BF_3{\cdot}Et_2O$. The compounds **1**,[3] **2**[3] and **4**[4] were identical with the corresponding naturally occurring compounds (mp, IR, UV and NMR).





1 R^1 = Me, R^2 = Me
2 R^1 = H, R^2 = Me
2a R^1 = H, R^2 = H

3 R^1 = H, R^2 = Me
3a R^1 = H, R^2 = H
4 R^1 = Me, R^2 = H



5 R^1 = NHCOMe, R^2 = $CH_2CH{=}C(Me)_2$
6 R^1 = NHC_6H_4-o-CO_2H, R^2 = $CH_2CH{=}C(Me)_2$

Footnotes

† Maximum overall[4] yield reported so far is 22%.

‡ Transformation of the substituted aniline (from **5**) into 4-hydroxy-5,7-dimethoxy-8-(3-methylbut-2-enyl)-2-quinolinone through the Conrad–Limpach reaction and its further elaboration to 4,5,7-trihydroxy-8-(3-methylbut-2-enyl)-coumarin is being currently pursued.

§ *Selected data* for **5**: ^{1}H NMR ($CDCl_3$) δ 1.78 (3 H, s), 1.82 (3 H, s), 2.06 (3 H, s), 3.28 (2 H, d, *J* 7 Hz), 3.8 (3 H, s), 3.82 (3 H, s), 4.18 (1 H, br, exchangeable with D_2O), 5.14 (1 H, m), 6.25 (1 H, d, *J* 3 Hz), 7.32 (1 H, d, *J* 2 Hz); ^{13}C NMR ($CDCl_3$) δ 170.19, 160.55, 159.55, 139.33, 133.55, 123.9, 114.25, 100.75, 96.89, 56.38, 55.42, 29.86, 25.52, 22.62, 17.9. For **6**: ^{1}H NMR($CDCl_3$) δ 1.66 (3 H, s), 1.72 (3 H,s), 3.35 (2 H, d, *J*7 Hz), 3.78 (3 H, s), 3.84 (3 H, s), 5.1 (1 H, m) 6.2 (1 H, d, *J* 3.7 Hz), 6.58 (1 H, d, *J* 3.7 Hz), 6.9 (1 H, br, exchangeable with D_2O), 8.18 (1 H, dd, *J* 8, 2 Hz), 9.1 (1 H, s, br, exchangeable with D_2O). For **3a**: ^{1}H NMR($CDCl_3$) δ 1.69 (3 H, s), 1.84 (3 H, s), 3.59 (2 H, d, *J* 7 Hz), 5.16 (1 H, m), 6.24 (1 H, s), 7.4–7.9 (3 H, m), 8.12 (1 H, dd, *J* 8, 2 Hz), 9.2 (1 H, s, br, exchangeable with D_2O), 13.5 (1 H, s, exchangeable with D_2O).

References

1 For reviews see: J. P. Michael, *Nat. Prod. Rep.*, 1991, 53; 1992, 25; 1993, 99; 1994, 163; 1995, 77.
2 J. Reisch, I. Mester and M. E. M. Aly, *J. Chem. Soc., Perkin Trans. 1*, 1983, 219.
3 R. C. Anand and A. K. Sinha, *J. Chem. Soc., Perkin Trans. 1*, 1991, 2339.

4 D. G. Loughhead, *J. Org. Chem.*, 1990, **55**, 2245 and references cited therein.
5 A. Elomri, S. Michael, F. Tillequim, K. Francois and M. Koch, *Heterocycles*, 1992, 799.
6 J. Reisch, P. Dziemba and T. Adam, *J. Heterocycl. Chem.*, 1993, 1469; J. Reisch, P. Dziemba, M. Lamura and A. R. R. Rao, *J. Heterocycl. Chem.*, 1993, 981.
7 R. D. H. Murray, J. Mendez and S. A. Brown, *The Natural Coumarins, Occurrence, Chemistry and Biochemistry*, Wiley-Interscience, New York, 1982.
8 R. A. Scherrer and H. R. Beatty, *J. Org. Chem.*, 1980, **45**, 2127.

Received, 20th September 1995; Com. 5/06211J