Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron Letters 47 (2006) 7741–7743
Tetrahedron Letters

Chemical and enzymatic synthesis of buprestin A and B—bitter acylglucosides from Australian jewel beetles (Coleoptera: Buprestidae)

Sabine Schramm,[a] Konrad Dettner[b] and Carlo Unverzagt[a,*]

[a]*Bioorganische Chemie, Gebäude NWI, Universität Bayreuth, 95440 Bayreuth, Germany*
[b]*Tierökologie II, Gebäude NWI, Universität Bayreuth, 95440 Bayreuth, Germany*

Received 21 July 2006; revised 21 August 2006; accepted 25 August 2006

Abstract—A chemical and enzymatic synthesis was developed for buprestin A and B originally isolated from Australian jewel beetles (Coleoptera: Buprestidae). The common motif of both acylglucosides is a β-D-glucopyranose-1,2-bis(pyrrole-2-carboxylate). Starting from 1,3,4,6-tetra-*O*-acetyl-α-D-glucose, the first pyrrole-2-carboxylate was introduced by DCC–DMAP mediated esterification. After conversion to a trichloroacetimidate the anomeric pyrrole-2-carboxylate was installed. Selective removal of the acetates was accomplished using immobilized *Candida antarctica* lipase. The resulting triol was converted to Buprestin A or B via a Mitsunobu reaction.
© 2006 Elsevier Ltd. All rights reserved.

Two publications describe the isolation and structural characterization of two acylglucosides containing multiple pyrrole-2-carboxylic acid residues in Australian jewel beetles (Buprestidae).[1] The compounds named buprestin A and B (Fig. 1) were purified and structurally characterized by NMR. The compounds were found to act as deterrents for ants, suggesting a biological role of the buprestins.[2] To further investigate the biological properties of the buprestins and related compounds, we developed a synthetic approach based on chemical and enzymatic methods. This approach should provide sufficient amounts of the reference compounds for structure confirmation and biological assays. Since both buprestins differ only in the residue attached to O-6, the use of a common intermediate was desirable. We herein describe the synthesis of buprestin A and B from a common precursor.

Retrosynthetic analysis (Fig. 1) suggested the introduction of the variable acyl residue at O-6 in the last step. This would also allow the attachment of alternative residues at O-6, which may be present in minor buprestins. The desired precursor (triol **6**) contains a pyrrole-2-carboxylic acid moiety at O-2 and at the anomeric center. In order to exploit the anticipated neighboring group activity of the 2-*O*-pyrrole-2-carboxylic acid group, this residue should be installed first, thus leading to the glucose-tetraacetate **1**,[3] which is available in a one-pot reaction starting from glucose. It was first examined how to esterify pyrrole-2-carboxylic acid with OH-2 of compound **1**. Initial attempts to generate the ester at O-2 using pyrrole-2-trichloromethylketone[4] and compound **1** activated with DBU or NaH gave low yields due to the instability of **1**. A suitable method was found using dicyclohexylcarbodiimide (DCC) and *N*,*N*-dimethylaminopyridine (DMAP) giving the desired ester **2** in 93% yield. To avoid the separation of anomers resulting from the acylation of anomeric hydroxyl groups,[5] the β-selective introduction of the anomeric pyrrole-2-carboxylic acid was investigated using the trichloroacetimidate[6] method. As a model compound 2,3,4,6-tetra-*O*-acetyl-α-D-glucosyltrichloroacetimidate[6] was reacted with pyrrole-2-carboxylic acid in methylene chloride. Glycosyltrichloroacetimidates react with benzoic acid without activation,[7] whereas pyrrole-2-carboxylic acid was only incorporated when BF_3–Et_2O was added as an activator to give the desired 1-*O*-pyrrole-2-carboxylated β-glucoside in 72% yield (data not shown). According to this

Keywords: Acylglucoside; Buprestidae; Lipase; Carbohydrate; Pyrrole-2-carboxylic acid.
* Corresponding author. Tel.: +49 921 552670; fax: +49 921 555365; e-mail: carlo.unverzagt@uni-bayreuth.de

0040-4039/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2006.08.119

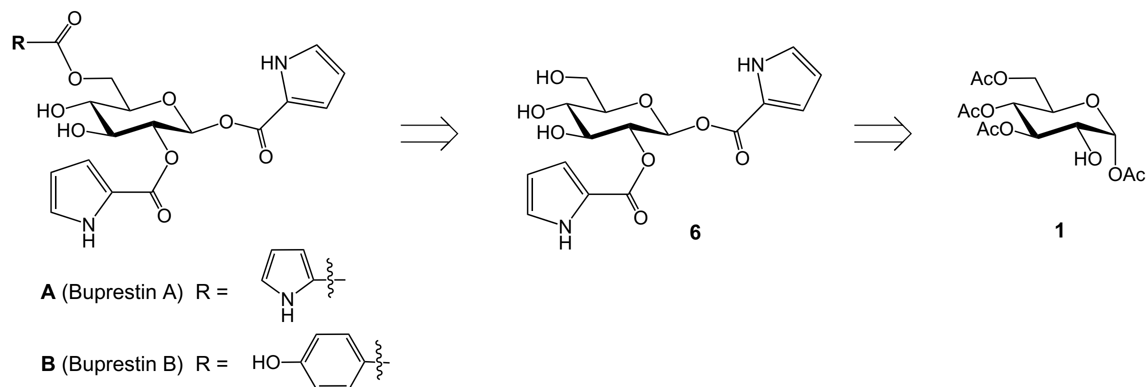

Figure 1. Retrosynthetic analysis of buprestin A and B leading to the common precursor **6**.

approach, compound **2** was first converted to hemiacetal **3** by removal of the anomeric acetate with hydrazine acetate[8] (73%) followed by the addition of trichloroacetonitrile in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (81%). When reacting imidate **4** with pyrrole-2-carboxylic acid in the presence of BF_3–Et_2O, acylglucoside **5** was obtained in 89% yield (Fig. 2). The pyrrole-2-carboxylate moiety at O-2 gave only the β-product resulting from neighboring group participation. With compound **5** in hands, removal of the three acetates to the envisioned universal precursor **6** was investigated. It was found by TLC analysis that the reaction of **5** with solid K_2CO_3 in CH_2Cl_2/MeOH (2:1) led to numerous deacylation products. After 30% conversion, the desired compound **6** was present in approximately 15%. Prolonged reaction time gave rise to hemiacetals and glucose. When attempting the deacetylation using catalytic NaOMe in MeOH, the yield of **6** could be increased to 30–40% (TLC). The yields remained unsatisfactory due to a comparable reactivity of the acetates and the anomeric acyl group. Thus, a selective deprotection[9] under neutral conditions was investigated using hydrolytic enzymes. A panel of twelve commercially available lipases was tested with **5** as a substrate. Using LC-MS analysis, only the lipase from *Candida antarctica* (CAL B; Novozym 435) showed sufficient activity.[10] With this enzyme, the conditions of deacetylation were improved stepwise yielding the desired triol **6** in an optimized yield of 86% after flash chromatography. A side product resulting from acyl group migration[11] onto O-3 was identified as compound **7** (8% yield).

Compound **6** was used to install the third acyl group at O-6. Initial attempts to selectively obtain an O-6 acylated product by reacting activated pyrrole-2-carboxylic acid (DCC–DMAP) gave only low yields (19%) along with an O-4-regioisomer and products carrying multiple acylations. Selective introduction at O-6 was successfully accomplished using the Mitsunobu reaction[12] (triphenylphosphine, diethylazodicarboxylate (DEAD)) giving buprestin A (**A**) in 72% yield. The ^{1}H and ^{13}C NMR data of the synthetic material[13] are in accordance with the published data, thus confirming the structure of buprestin A proposed by Moore and co-workers.[1]

The Mitsunobu reaction was also applied to introduce *p*-hydroxybenzoic acid directly, however, the yield was only 22%. Thus, *p*-acetoxybenzoic acid was used giving the O-acetylated buprestin B derivative **8** (75%)

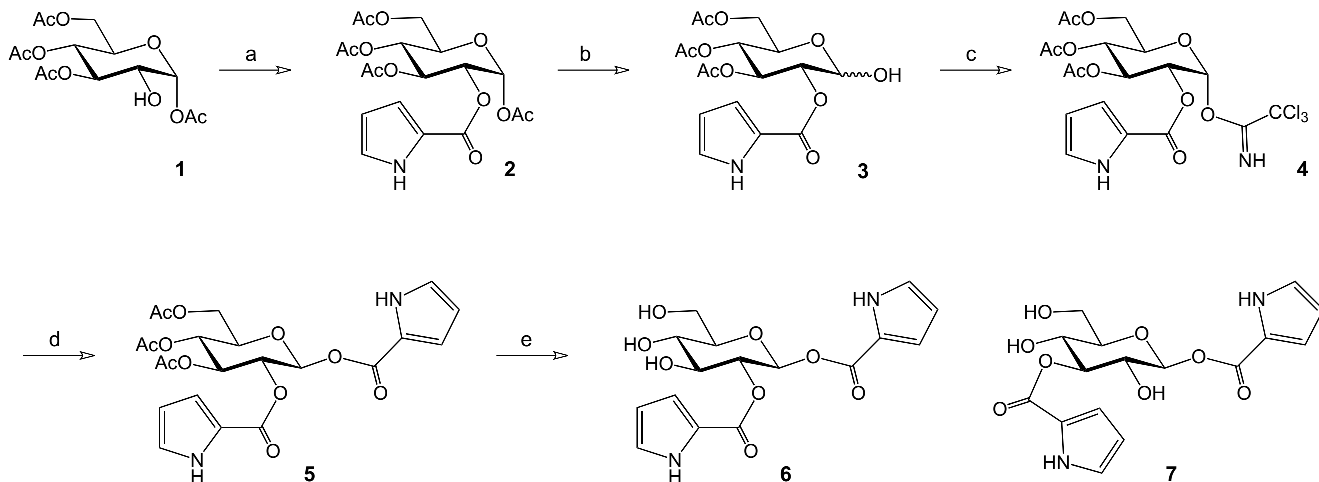

Figure 2. (a) Pyrrole-2-carboxylic acid, DCC, DMAP, CH_2Cl_2, (93%); (b) hydrazine acetate, DMF (73%); (c) Cl_3CCN, DBU, CH_2Cl_2, 0 °C (81%); (d) pyrrole-2-carboxylic acid, BF_3–OEt_2, molecular sieves 4 Å, CH_2Cl_2, 0 °C (89%); (e) *Candidia antarctica* lipase B, immobilized (Novozym 435), 0.5 M NH_4OAc/CH_3CN (9:1), 40 °C, (**6**: 86%), (**7**: 8%).

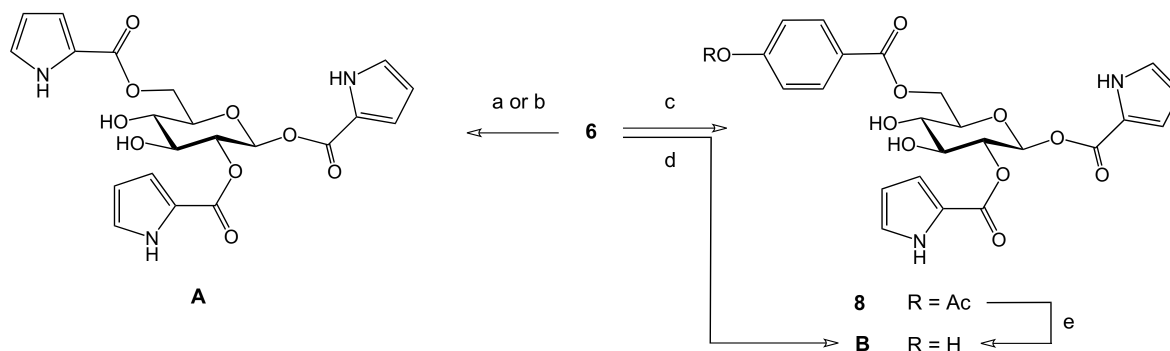

Figure 3. (a) Pyrrole-2-carboxylic acid, DCC, DMAP, THF, (19%); (b) pyrrole-2-carboxylic acid, PPh_3, DEAD, THF, (72%); (c) *p*-hydroxybenzoic acid, PPh_3, DEAD, THF, (22%); (d) *p*-acetoxybenzoic acid, PPh_3, DEAD, THF, (75%); (e) *Candidia antarctica* lipase B, immobilized (Novozym 435), 0.5 M NH_4OAc/CH_3CN (9:1), 40 °C, (90%).

(Fig. 3). Deprotection[10] of the phenolic acetate was achieved with immobilized CAL B leading to the desired buprestin B (**B**) in 90% yield after 30 min of reaction time. The NMR data[13] of the synthetic buprestin B are in accordance with the data published for the isolated compound.

In summary, a short synthesis was developed for buprestin A (six steps, 30% total yield) and for buprestin B (seven steps, 28% total yield). The analytical data for both compounds proved identical with the isolated material, thus confirming the structural assignment. With several hundred milligrams of the synthetic compounds in hand, biological assays will be conducted to further investigate the role of buprestins as chemical defense molecules in detail.

Acknowledgements

We are grateful to the Deutsche Forschungsgemeinschaft (DFG) Graduate College 678 and the Fonds der Chemischen Industrie for financial support.

References and notes

1. Brown, W. V.; Jones, A. J.; Lacey, M. J.; Moore, B. P. *Aust. J. Chem.* **1985**, *38*, 197–206.
2. Moore, B. P.; Brown, W. V. *J. Aust. Ent. Soc.* **1985**, *24*, 81–85.
3. Helferich, B.; Zirner, J. *Ber.* **1962**, *95*, 2604–2611.
4. Harbuck, J. W.; Rapoport, H. *J. Org. Chem.* **1972**, *37*, 3618–3622.
5. Perrie, J. A.; Harding, J. R.; Holt, D. W.; Johnston, A.; Meath, P.; Stachulski, A. V. *Org. Lett.* **2005**, *7*, 2591–2594.
6. Schmidt, R. R.; Kinzy, W. *Adv. Carbohydr. Chem. Biochem.* **1994**, *50*, 21–123.
7. Schmidt, R. R. *Angew. Chem.* **1986**, *98*, 213–236.
8. Excoffier, G.; Gagnare, D.; Utille, J. P. *Carbohydr. Res.* **1975**, *39*, 368–373.
9. Kadereit, D.; Waldmann, H. *Chem. Rev.* **2001**, *101*, 3367–3396.
10. Lambusta, D.; Nicolosi, G.; Patti, A.; Sanfilippo, C. *J. Mol. Catal. B: Enz.* **2003**, *22*, 271–277.
11. Tsuda, Y.; Yoshimoto, K. *Yuki Gosei Kagaku Kyokaishi* **1984**, *42*, 479–492.
12. Mitsunobu, O. *Synthesis* **1981**, 1–28.
13. Analytical data for buprestin A (**A**): ESI-MS (CH_3CN/H_2O, 0.1% formic acid): $C_{21}H_{21}N_3O_9$ M_r (calcd) 459.13, M_r (found) 482.25 $(M+Na)^+$, $R_f = 0.27$ (cyclohexane/ethyl acetate 1:2); $[\alpha]_D^{23}$ −65.0 (0.5, MeOH); ^{1}H NMR (270 MHz, DMSO-d_6): $\delta = 11.98$ (s, 1H, NH), 11.90 (s, 1H, NH), 11.87 (s, 1H, NH), 7.06–7.01 (m, 2H, Ar), 6.98 (m, 1H, Ar), 6.80 (m, 1H, Ar), 6.75 (m, 1H, Ar), 6.71 (m, 1H, Ar), 6.18 (m, 1H, Ar), 6.14–6.10 (m, 2H, Ar), 5.85 (d, $J_{1,2} = 8.5$ Hz, 1H, H-1), 5.59–5.53 (m, 2H, OH-3, OH-4), 5.04 (dd, $J_{1,2} = 8.5$ Hz, $J_{2,3} = 8.9$ Hz, 1H, H-2), 4.52 (dd, $J_{gem} = 11.7$ Hz, $J_{5,6a} < 1$ Hz, 1H, H-6a), 4.29 (dd, $J_{gem} = 11.7$ Hz, $J_{5,6b} = 5.3$ Hz, 1H, H-6b), 3.82–3.65 (m, 2H, H-5, H-3), 3.52 (m, 1H, H-4), ^{13}C NMR (67.5 MHz, DMSO-d_6): $\delta = 160.2$, 159.3, 158.4 (C=O Pyrr), 125.6 (Ar), 124.2 (2C, Ar), 121.6, 121.5, 120.4 (C_i–Ar), 116.4 (Ar), 115.3 (2C, Ar), 109.8 (Ar), 109.5 (2C, Ar), 91.9 (C-1), 74.9 (C-5), 73.6 (C-3), 72.2 (C-2), 69.7 (C-4), 62.6 (C-6).
Analytical data for buprestin B (**B**): ESI-MS (CH_3CN/H_2O, 0.1% formic acid): $C_{23}H_{22}N_2O_{10}$ M_r (calcd) 486.13, M_r (found) 509.29 $(M+Na)^+$, $R_f = 0.42$ (dichloromethane/methanol 1:2); $[\alpha]_D^{23}$ −64.7 (0.5, MeOH); ^{1}H NMR (270 MHz, DMSO-d_6): $\delta = 11.97$ (s, 1H, NH), 11.87 (s, 1H, NH), 10.35 (s, 1H, OH–Ph), 7.81 (d, $^3J = 8.7$ Hz, 2H, Ph-2/6), 7.02 (m, 1H, Pyr), 6.97 (m, 1H, Pyr), 6.86 (d, $^3J = 8.7$ Hz, 2H, Ph-3/5), 6.74 (m, 1H, Pyr), 6.70 (m, 1H, Pyr), 6.14–6.08 (m, 2H, Pyr), 5.85 (d, $J_{1,2} = 8.4$ Hz, 1H, H-1), 5.60 (d, $J_{OH,4} = 5.7$ Hz, 1H, OH-4), 5.55 (d, $J_{OH,3} = 5.7$ Hz, 1H, OH-3), 5.00 (dd, $J_{1,2} = 8.4$ Hz, $J_{2,3} = 9.1$ Hz, 1H, H-2), 4.50 (dd, $J_{gem} = 11.9$ Hz, $J_{5,6a} < 1$ Hz, 1H, H-6a), 4.31 (dd, $J_{gem} = 11.9$ Hz, $J_{5,6b} = 5.1$ Hz, 1H, H-6b), 3.79 (m, 1H, H-5), 3.69 (m, 1H, H-3), 3.49 (m, 1H, H-4), ^{13}C NMR (67.5 MHz, DMSO-d_6): $\delta = 165.4$ (C=O Ph), 162.0 (Ph-4), 159.3, 158.4 (C=O Pyr), 131.5 (Ph-2/6), 125.5 (Pyr), 124.2 (Pyr), 121.5, 120.4 (C_i–Pyr), 120.2 (Ph-1), 116.4 (Pyr), 115.3 (3C, Pyr, Ph-3/5), 109.8 (Pyr), 109.4 (Pyr), 91.9 (C-1), 74.8 (C-5), 73.6 (C-3), 72.2 (C-2), 69.7 (C-4), 63.1 (C-6).