Synlett G. Smits, R. Zemribo Letter

One-Step Preparation of Pyrrolo[1,4]benzodiazepine Dilactams: Total Synthesis of Oxoprothracarcin, Boseongazepines B and C

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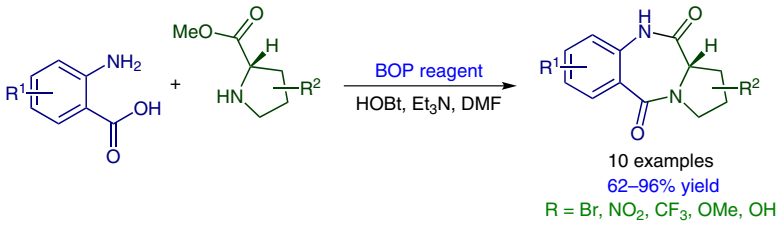


Received: 07.05.2015
Accepted after revision: 03.07.2015
Published online: 01.09.2015
DOI: 10.1055/s-0034-1378877; Art ID: st-2015-d0345-l

Abstract A one-step synthesis of pyrrolo[1,4]benzodiazepine dilactams has been developed. The high yielding method involves direct coupling of unprotected anthranilic acids with proline esters. This transformation was successfully applied in the first total syntheses of boseongazepines B and C as well as oxoprothracarcin and limazepine E.

Key words pyrrolo[1,4]benzodiazepine, dilactams, total synthesis, oxoprothracarcin, boseongazepine

Pyrrolo[1,4]benzodiazepines (PBD's) **1** are naturally occurring tricyclic antitumor antibiotics, possessing an *S*-configuration chiral center at C11a, resulting in right-handed twist of the molecule (Figure 1). The first PBD class member, anthramycin (**2**)[1] was isolated in 1968 by Leimgruber et al. and immediately attracted the attention of scientific community due to its interesting biological properties. It was found that PBD's covalently bind to C-2 amino group of guanine residues within the minor groove of DNA.[2] Nowdays a significant amount of information[3] (over 200 publications and 40 patents) on PBD's can be found in the scientific literature. The reports include the isolation of new natural products, novel synthetic pathways, as well as new applications of PBD's. Furthermore, one PBD class member, SJG-136 is in Phase II clinical trials for treating ovarian carcinoma.[4]

PBD dilactams, containing the oxidized N10-C11 amidic moiety have become popular due to their robustness towards a number of synthetic transformations and nowadays several protocols for conversion of the N10-C11 amide functionality to the DNA-alkylating imine function are known.[3d] Furthermore, in the past decade there has been a

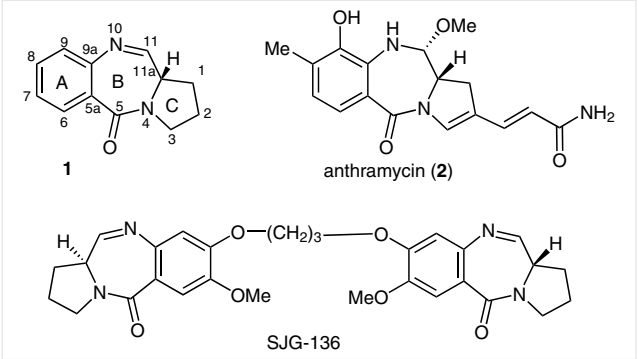


Figure 1 Representative PBD structures

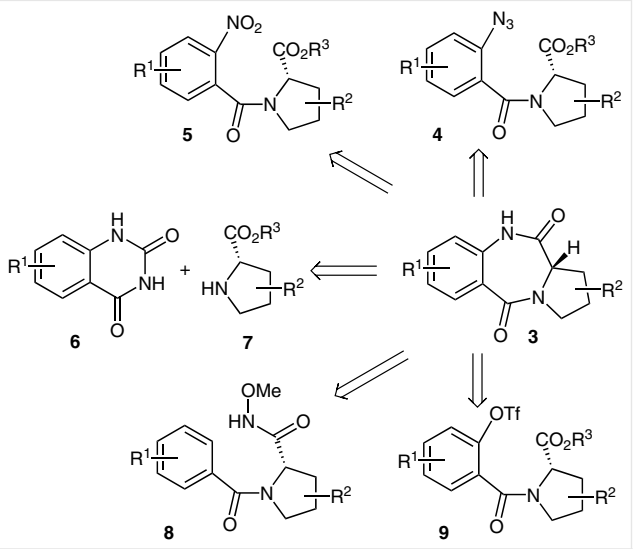
growing interest in PBD dilactams themselves, since they have shown interesting biological activity towards several different targets.[5]

The published protocols for the synthesis of the PBD dilactam skeleton usually consist of several synthetic steps.[3a] Typically, the last step of PBD dilactam **3** synthesis is the B-ring formation of prefunctionalized substrates (Scheme 1).

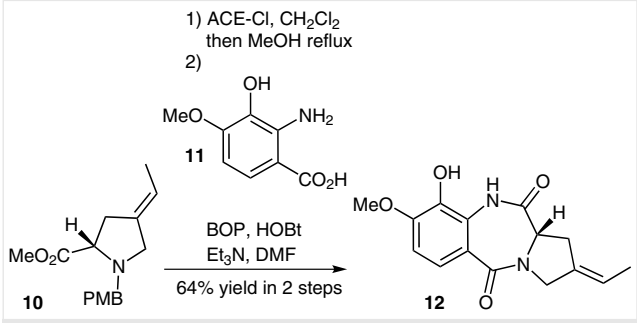
Classical methods include a reductive cyclization of azidoesters **4** or nitroesters **5**, or a condensation of proline esters **7** with isatoic anhydrides **6**. Furthermore, PBD dilactams can also be obtained via transition-metal-catalyzed processes (**8** and **9**).

The number of synthetic steps as well as the harsh conditions and reagents used in published protocols encouraged us to develop an alternative protocol for the synthesis of PBD dilactams.

In our previous studies[6] we found that PBD dilactam **12** could be readily synthesized in a two-step sequence by first cleaving the nitrogen protecting group of proline **10**, followed by coupling the intermediate proline ester hydrochloride to the corresponding unprotected anthranilic acid



Scheme 1 Retrosynthetic analysis of PBD dilactams[3a]



Scheme 2 Synthesis of dilactam **12**; ACE-Cl = 1-chloroethyl chloroformate; BOP = (benzotriazol-1-yloxy)tris(dimethylamino)phosphonium hexafluorophosphate; HOBt = 1-hydroxybenzotriazole hydrate

11 (Scheme 2). These noteworthy results directed us to study the scope and limitations of this novel method for the synthesis of PBD dilactams. Herein we report an efficient method for the synthesis of PBD dilactams in a single step from unprotected anthranilic acids and proline esters.

A number of commercially available anthranilic acids and proline esters were examined for the synthesis of the corresponding PBD dilactams, and the results are shown in Table 1.

Table 1 Synthesis of PBD Dilactams

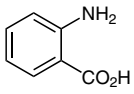
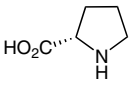
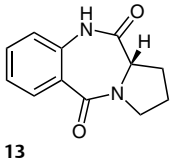
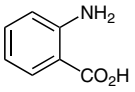
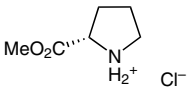
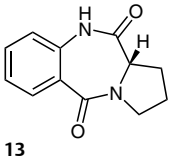
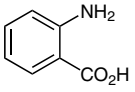
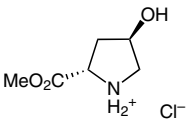
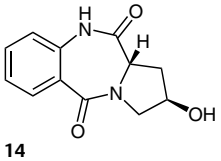
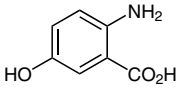
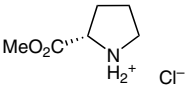
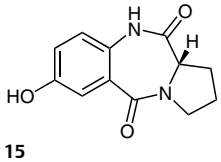
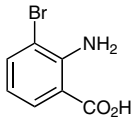
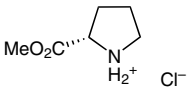
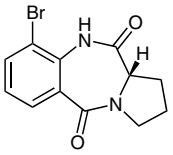
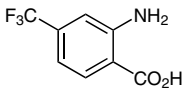
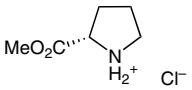
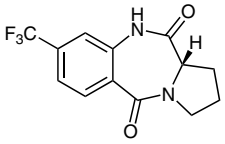
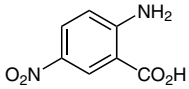
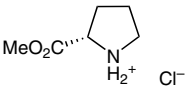
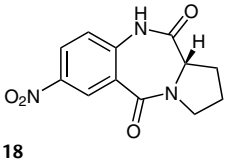
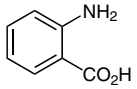
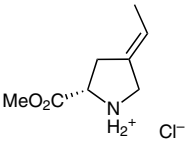
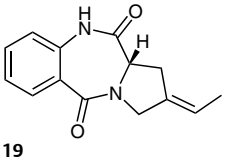
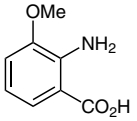
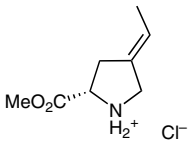
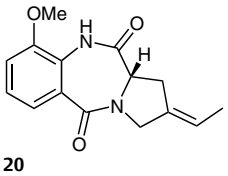
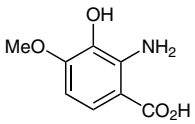
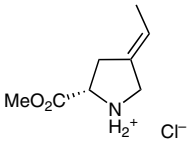
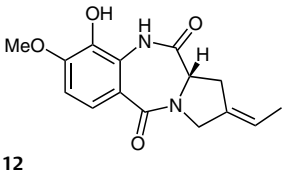
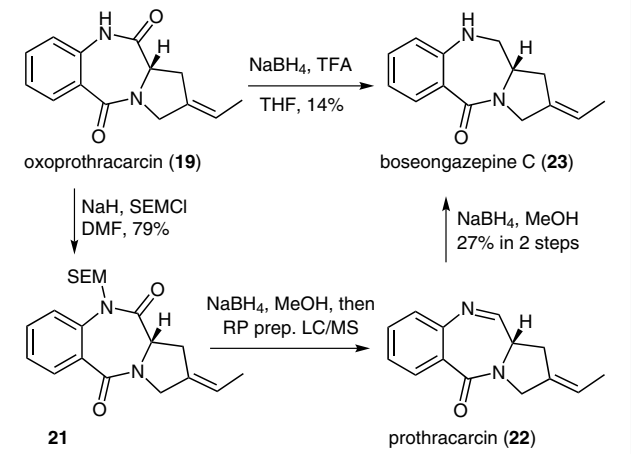
Entry	Anthranilic acid	Proline derivative	Product	Yield (%)
1			 **13**	71
2			 **13**	92[a]
3			 **14**	61[a]
4			 **15**	68

Table 1 (continued)

Entry	Anthranilic acid	Proline derivative	Product	Yield (%)
5			 **16**	96[a]
6			 **17**	96[a]
7			 **18**	92[a]
8			 **19**	73[a,b]
9			 **20**	62[a,b]
10			 **12**	64[b]

[a] Cat. HCl in THF–H_2O was necessary to effect the cyclization.
[b] Yield in three steps, including the PMB protecting group cleavage of the proline nitrogen using ACE-Cl.[7]

After optimization of the reaction conditions initially found, the best results were obtained using BOP as the amide coupling reagent in combination with HOBt·H_2O and Et_3N in DMF.[8] The transformation generally proceeds with good yields of up to 96% (Table 1, entries 5 and 6) and a number of functional groups are tolerated; even unprotected hydroxyl groups (Table 1, entry 3) and phenol groups (Table 1, entries 4 and 10). Unprotected proline also could serve as a coupling partner (Table 1, entry 1). However higher yields were obtained by using a proline ester (Table 1, entry 2). In contrast, the reported methods for the synthesis of these PBD dilactams often contain multistep synthesis (six steps in case of **15**[9]) or harsh reaction conditions (several hours at 120 °C–150 °C in DMSO in case of **13**,[10] **14**[11] and **18**[12]). The transformation was also applicable to the total synthesis of two natural products, namely, boseongazepine B[13] (**20**) and oxoprothracarcin[14] (**19**) as well as the key intermediate **12** used in the total synthesis of limazepine E.[6] Oxoprothracarcin (**19**) was selectively transformed into boseongazepine C (**23**) by reduction of the N10-C11 amide group (Scheme 3).



Scheme 3 Total synthesis of boseongazepine C

The reported method[15] for selective reduction of the N10-C11 amide group gave very low yields of the desired boseongazepine C (**23**) and the reaction was also not reproducible. A reduction of the double bond was also observed using these conditions. To increase the yield of the reduction we applied the described[3d] concept by introducing an N10 nitrogen protecting group to lower the electron density on nitrogen N10, thereby increasing the electrophilicity of the C11-carbonyl. Although the N10 protecting group was successfully installed, the subsequent reduction sequence was again low yielding. Nevertheless, the spectroscopic data of boseongazepine C (**23**) obtained by either reduction method were in a good agreement with the literature data.

In summary, we have developed a convenient and high yielding method for the synthesis of pyrrolo[1,4]benzodiazepine dilactams in one step from unprotected anthranilic acids and proline ester derivatives. Notably, a number of functional groups are tolerated, even unprotected hydroxyl and phenol groups. The broad number of commercially available proline esters and anthranilic acids makes this method a valuable tool for the synthesis of large PBD dilactam libraries in short time.

Acknowledgment

We thank the European Social Fund (ESF) for financial support (project No. 1DP/1.1.1.2.0/13/APIA/VIAA/003).

Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0034-1378877.

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(4) See: https://clinicaltrials.gov/show/NCT01200797.
(5) (a) Jiao, R. H.; Xu, H.; Cui, J. T.; Ge, H. M.; Tan, R. X. *J. Appl. Microbiol.* **2013**, *114*, 1046. (b) Antonow, D.; Jenkins, T. C.; Howard, P. W.; Thurston, D. E. *Bioorg. Med. Chem.* **2007**, *15*, 3041. (c) Kamal, A.; Reddy, K. L.; Devaiah, V.; Shankaraiah, N.; Reddy, G. S. K.; Raghavan, S. *J. Comb. Chem.* **2007**, *9*, 29. (d) Biel, M.; Deck, P.; Giannis, A.; Waldmann, H. *Chem. Eur. J.* **2006**, *12*, 4121.
(6) Smits, G.; Zemribo, R. *Org. Lett.* **2013**, *15*, 4406.
(7) Yang, B. V.; O'Rourke, D.; Li, J. *Synlett* **1993**, 195.
(8) **General Procedure for Synthesis of PBD Dilactams**: To a stirred solution of anthranilic acid (2.2 mmol, 2 equiv), BOP reagent (2.2 mmol, 2 equiv) and HOBt hydrate (2.2 mmol, 2 equiv) in anhyd DMF (10 mL) was added Et_3N (10.9 mmol, 10 equiv). After stirring for 15 min, proline ester hydrochloride (1.1 mmol, 1 equiv) was added and the resultant mixture was stirred for 16 h. The volatiles were removed in vacuo and the residue was partitioned between CH_2Cl_2 and brine. The organic phase was dried over anhyd Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by flash column chromatography (EtOAc–MeOH) or reversed-phase flash column chromatography (MeOH + 0.5% HCOOH–H_2O + 0.5% HCOOH).
(*S*)-9-Bromo-2,3-dihydro-1*H*-benzo[*e*]pyrrolo[1,2-*a*][1,4]-diazepine-5,11(10*H*,11a*H*)-dione (23): colorless solid; $[\alpha]_D$ +423 (*c* = 0.1, MeOH). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.95 (d, *J* = 7.9 Hz, 1 H), 7.69–7.81 (m, 2 H), 7.14 (t, *J* = 7.9 Hz, 1 H), 4.05 (d, *J* = 6.2 Hz, 1 H), 3.76–3.91 (m, 1 H), 3.50–3.70 (m, 1 H), 2.67–2.86 (m, 1 H), 1.92–2.18 (m, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.0, 164.4, 136.0, 133.1, 130.9, 129.2, 126.0, 115.5, 56.8, 47.5, 26.4, 23.5. HRMS–ESI: *m*/*z* [M + H] calcd for $C_{12}H_{12}N_2O_2Br$: 295.0082; found: 295.0090.
(*S*)-8-(Trifluoromethyl)-2,3-dihydro-1*H*-benzo[*e*]pyrrolo-[1,2-*a*][1,4]diazepine-5,11(10*H*,11a*H*)-dione (24): yellowish solid; Lit. 9: $[\alpha]_D$ +41 (*c* = 0.1, MeOH). ^{1}H NMR (400 MHz, DMSO): δ = 7.93 (dd, *J* = 7.9, 1.5 Hz, 1 H), 7.76 (br s, 1 H), 7.73 (dd, *J* = 7.9, 1.5 Hz, 1 H), 7.12 (t, *J* = 7.9 Hz, 1 H), 4.03 (d, *J* = 6.0 Hz, 1 H), 3.72–3.88 (m, 1 H), 3.52–3.69 (m, 1 H), 2.66–2.85 (m, 1 H), 1.95–2.14 (m, 3 H). ^{13}C NMR (100 MHz, DMSO): δ = 170.7, 163.4, 137.1, 131.9, 131.9 (q, *J* = 32.2 Hz), 129. 8, 123.5 (q, *J* = 272.8 Hz), 119.9, 118.1, 56.1, 47.0, 25.7, 23.0. HRMS–ESI: *m*/*z* [M + H] calcd for $C_{13}H_{12}N_2O_2F_3$: 285.0851; found: 285.0855.
(*S*,*E*)-2-Ethylidene-10-{[2-(trimethylsilyl)ethoxy]methyl}-2,3-dihydro-1*H*-benzo[*e*]pyrrolo[1,2-*a*][1,4]diazepine-5,11(10*H*,11a*H*)-dione (21): To a stirred solution of oxoprothracarcin (140 mg, 0.6 mmol, 1 equiv) in anhyd DMF (1.5 mL) under an argon atmosphere was added NaH (80% in mineral oil, 21 mg, 0.7 mmol, 1.2 equiv) at 0 °C. After stirring for 30 min SEM-Cl (118 mg, 0.7, 1.2 equiv) was added and the mixture was allowed to warm to r.t. overnight and then partitioned between CH_2Cl_2 and brine. The organic phase was dried over anhyd Na_2SO_4, filtered and concentrated in vacuo. The residue was

purified by flash column chromatography (EtOAc–PE, 9:1 → 1:1). The title compound was isolated as a yellowish oil (170 mg, 79%); $[\alpha]_D$ +333.00 (*c* = 0.1, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.90 (dd, *J* = 7.8, 1.6 Hz, 1 H), 7.69 (dd, *J* = 7.8, 1.6 Hz, 1 H), 7.48–7.57 (td, *J* = 7.8, 1.6 Hz, 1 H), 7.34 (td, *J* = 7.8, 1.6 Hz, 1 H), 5.46–5.60 (m, 2 H), 4.72 (d, *J* = 9.8 Hz, 1 H), 4.24–4.40 (m, 2 H), 4.17 (d, *J* = 15.7 Hz, 1 H), 3.59–3.82 (m, 2 H), 3.48 (d, *J* = 16.3 Hz, 1 H), 2.55–2.70 (m, 1 H), 1.74 (d, *J* = 6.6 Hz, 3 H), 0.99 (t, *J* = 8.6 Hz, 2 H), 0.02 (s, 9 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.0, 165.3, 139.9, 133.1, 132.4, 130.0, 129.5, 126.4, 122.7, 118.5, 78.1, 67.1, 57.6, 51.1, 28.2, 18.4, 14.6, –1.3. HRMS–ESI: *m*/*z* [M + Na] calcd for $C_{20}H_{28}N_2O_3SiNa$: 395.1767; found: 395.1758.

Boseongazepine C: To a stirred solution of **21** (150 mg, 0.4 mmol, 1 equiv) in MeOH (3 mL) was added $NaBH_4$ (46 mg, 1.2 mmol, 3 equiv) at 0 °C. The mixture was then stirred at r.t. and then an additional 2 equiv of $NaBH_4$ were added. The process of addition (2 equiv of $NaBH_4$) was repeated three times to achieve full consumption of **21**. The reaction mixture was then partitioned between CH_2Cl_2 and brine. The organic phase was separated and the aq phase was extracted with CH_2Cl_2 (2 ×). The combined organic extracts were dried over anhyd Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by preparative LC–MS (MeOH + 0.5% HCOOH–H_2O + 0.5% HCOOH). The collected prothracarcin was used in the next step without further purification. The obtained material was dissolved in a mixture of MeOH (1 mL) and CH_2Cl_2 (0.3 mL) and treated with $NaBH_4$ (46 mg, 1.208 mmol, 3 equiv). The process was repeated several times to achieve full consumption of the prothracarcin. The reaction mixture was then partitioned between CH_2Cl_2 and brine. The organic phase was separated and the aq. Phase was extracted with CH_2Cl_2 (2 ×). The combined organic extracts were dried over anhyd Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by flash column chromatography (EtOAc–PE, 1:1 → 1:0). The title compound was isolated as a yellowish solid (25 mg, 27%). See the Supporting Information for compound characterization.

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