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A Novel Route to Pyrrolo[2,1-*c*][1,4]benzodiazepin-5-ones. Formal Total Synthesis of (±)-DC-81

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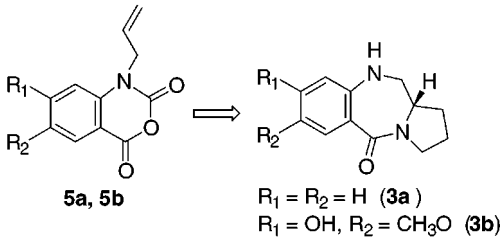
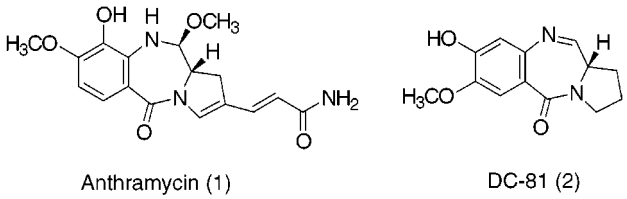
ABSTRACT



Compounds 3a and 3b were synthesized from N-allylisatoic anhydrides 5a and 5b in six and seven steps, respectively. Synthesis of 3b constitutes a formal total synthesis of (±)-DC-81.

Currently there is considerable interest in the discovery and development of small molecules such as pyrrolo[2,1-*c*][1,4]-benzodiazepines (PBD's) as potential antitumor and gene targeted drugs.[1] The PBD class of antitumor antibiotics exert their biological activity by covalently binding to the N-2 of guanine in the minor groove of DNA through the imine or imine equivalent functionality at N10−C11 of the PBD's. Anthramycin (**1**) and DC-81 (**2**) are two well-known and promising members of the PBD's (Figure 1). Synthetic

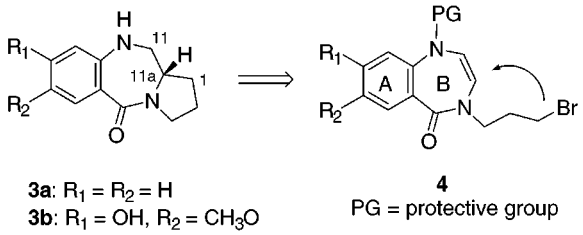


Anthramycin (1) DC-81 (2)

Figure 1.

approaches to PBD's have been documented.[2,3] Herein we would like to introduce a novel, linear approach for the total synthesis of PBD. The key feature of our synthesis is based on the pyrrolidine C-ring formation from radical-initiated carbon−carbon bond formation of the C1−C11a bond from **4** (Scheme 1).

Scheme 1



3a: $R_1 = R_2 = H$
3b: $R_1 = OH$, $R_2 = CH_3O$

4
PG = protective group

The *N*-allylisatoic anhydrides **5a** and **5b** were chosen as our starting materials. While **5a** is commercially available,[4]

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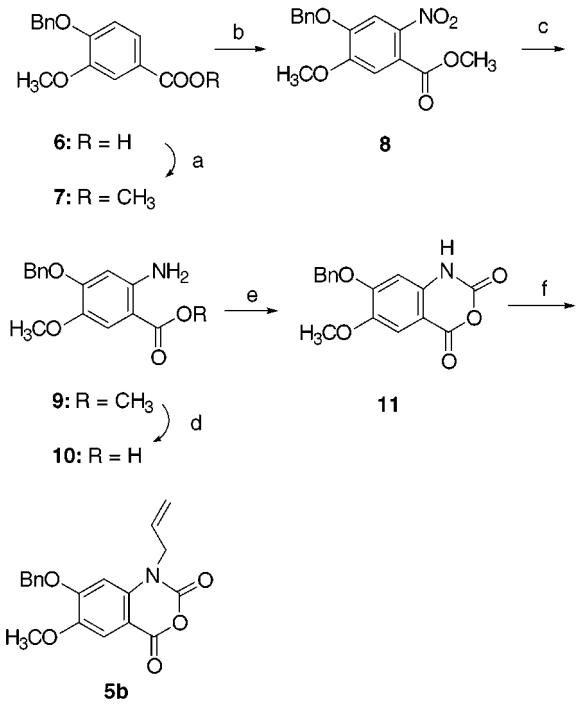
5b[5] was prepared from the known 4-benzyloxy-3-methoxybenzoic acid **6**[6] in six steps as shown in Scheme 2. Methyl ester **7**, which was obtained by esterification of **6**, was nitrated with fuming nitric acid to afford an 83% yield of methyl 4-benzyloxy-5-methoxy-2-nitrobenzoate **8**. The nitro group in **8** was cleanly reduced by sodium borohydride using nickel(II) chloride as catalyst to generate aniline **9**, which was converted to acid **10** by hydrolysis. The sodium salt of **10** was treated with a phosgene−toluene solution directly to give 7-benzyloxy-6-methoxyisatoic anhydride **11** as a solid after simple filtration. The desired *N*-allyl anhydride **5b** was then prepared by treatment of **11** with sodium hydride followed by allyl bromide in *N*,*N*-dimethylacetamide.[7]

The *N*-allylisatoic anhydrides (**5a** and **5b**) were reacted with 3-bromopropylamine hydrobromide in the presence of triethylamine as base (Scheme 3).[5] The purified allylamino benzamides **12** slowly self-condensed, as shown by nonpolar spot formation on TLC during chromatographic purification, and thus were directly protected as the stable trifluoro-

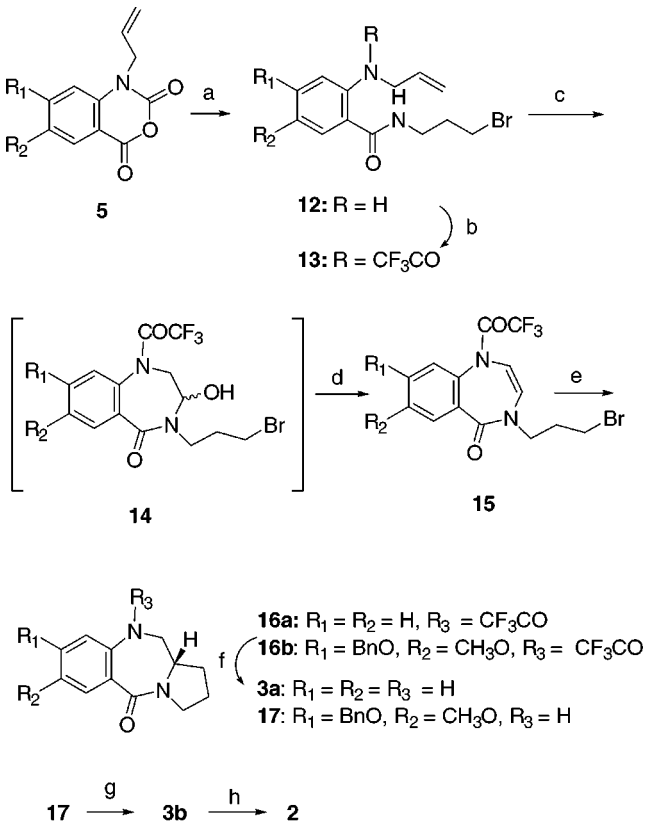
Scheme 2. Synthesis of **5b**[a]



[a] Conditions and yields: (a) CH_3I, K_2CO_3, acetone, reflux, 3 h, 59%. (b) fuming HNO_3,$SnCl_4$, CH_2Cl_2, -25°C, 10 min, 83%. (c) $NaBH_4$, $NiCl_2.6H_2O$, MeOH, CH_2Cl_2, 0-5°C,30 min, 96%. (d) aqueous NaOH, MeOH, reflux, 1h, 98%. (e) 2 N NaOH then phosgene, rt, 2 h, 79%. (f) sodium hydride then allyl bromide, DMA, rt,12 h, 87%

Scheme 3

For **5** and **12** to **16**: **a**: $R_1 = R_2 = H$; **b**: R_1 = BnO, $R_2 = CH_3O$



[a] Conditions and yields: (a) $Br(CH_2)_3NH_2.HBr$, Et_3N / CH_3CN, rt, 5 h. (b) TFAA, Et_3N / CH_2Cl_2, 0°C, 5 min, 79% for **13a** and 58% for **13b** over 2 steps. (c) O_3 then Me_2S, CH_2Cl_2, MeOH, -78°C. (d) CSA, refluxing toluene, 8 h, 69% for **15a** from **13a**, 45% for **15b** from **13b**. (e) Bu_3SnH, AIBN, benzene, reflux, 4 h, 90 % for **16a**, 91% for **16b**. (f) K_2CO_3 , MeOH, H_2O, rt, 12 h, 96% for **3a**, 95% for **17**. (g) NH_4CO_2H,10% Pd/C, MeOH, reflux, 1 h, 57%. (h) reference 3c

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(4) Purchased from Maybridge Inc.

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(6) Thurston, D. E.; Murty, V. S.; Langley, D. R.; Jones, G. B. *Synthesis* **1990**, 81.

(7) We followed the following literature for a similar reaction: Coppola, G.; Damon, R. E.; Hardtmann, G. E. *Synthesis* **1981**, 391.

acetamides **13**. The allylic double bond in **13** was subjected to ozonolysis followed by quenching with dimethyl sulfide. The resulting crude hemiaminal intermediates **14** were dehydrated in refluxing toluene with camphorsulfonic acid (CSA) as catalyst to afford the bicyclic enamides **15**. The pivotal step, the tributyltin hydride mediated radical cyclization of **15**, afforded the ring-closure tricyclic compounds **16** in excellent yields. The trifluoroacetyl groups were removed in methanolic aqueous potassium carbonate solution to yield the amino compounds **3a** and **17**. The benzyl protecting group in **17** was removed by palladium−carbon-catalyzed hydrogenation using ammonium formate as the hydrogen source to give **3b**. Since **3b** had already been converted to DC-81 (**2**) by Kamal and Thurston in a recently developed procedure,[3c] this synthesis constitutes a formal total synthesis of (±)-DC-81 (**2**).

In conclusion, using bicyclic benzodiazepinone intermediates **15**, we were able to generate a novel route to PBD's via radical cyclization to form the C1−C11a bond. This synthesis complements the known methodologies[2,3] for PBD synthesis and should provide entry to the synthesis of other naturally occurring PBD's and their analogues. This would be especially true for the synthesis of PBD's with additional C-ring functionalities, many of which are important for biological activity[1,8] (by starting with C2-substituted 3-bromopropylamine derivatives).

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Supporting Information Available: Full experimental procedures for syntheses and spectra data (IR, ^{1}H and ^{13}C NMR and MS) of **7**−**11, 5b, 13a, 13b, 15a, 15b, 16a, 16b, 17, 3a** and **3b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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