Tetrahedron Letters 52 (2011) 7000–7003

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

A new enantioselective approach to the core structure of hypoxia selective prodrugs related to the duocarmycins

Daniel M. Heinrich *, Jean-Jacques Youte, William A. Denny, Moana Tercel

Auckland Cancer Society Research Centre, Faculty of Medical and Health Sciences, The University of Auckland, Private Bag 92019, Auckland 1142, New Zealand

ARTICLE INFO

Article history:
Received 20 September 2011
Revised 7 October 2011
Accepted 18 October 2011
Available online 23 October 2011

Keywords:
Prodrug
Hypoxia
DNA alkylating
Duocarmycin
Enantioselective
Organocatalysis

ABSTRACT

The indoline scaffold of hypoxia selective prodrugs of DNA-alkylating agents related to the duocarmycin natural products was synthesized via an enantioselective Friedel–Crafts alkylation. Easily accessible starting materials and good stereoselectivity in the alkylation step provide an enantioselective synthesis of the DNA-alkylating subunit.

Cytotoxic drugs for cancer chemotherapy ideally need to be highly potent and very selective for cancer cells. The natural products yatakemycin,[1] the duocarmycins [see for example duocarmycin SA (**1**) in Fig. 1] and CC-1065 are well known for their very potent cytotoxic activity and are therefore of interest as potential candidates for anticancer drug development.[2–4] They consist of a spirocyclic subunit that sequence-specifically alkylates AT-rich sites of the minor groove of DNA. Alkylation of N3 of adenine generates long-lived adducts that ultimately leads to apoptosis of the affected cells. Unfortunately, the natural products are not very selective for cancer cells. Thus, two of the duocarmycin analogues, carzelesin and adozelesin that progressed to clinical trials failed due to lack of specificity.[5–8] Improving the selectivity of drugs related to the duocarmycins has become a priority for researchers world-wide.[2,9,10] One approach to this has been the prodrug concept, where a non-toxic prodrug form is administered and transported through the vascular system to reach the targeted cancer cells, where it exploits a particular condition present in the cancer tissue to activate the drug.

One such cancer-specific condition is that many solid tumours are oxygen deprived (hypoxic) due to their high turnover number related to the malignant growth and the poor development of tu-

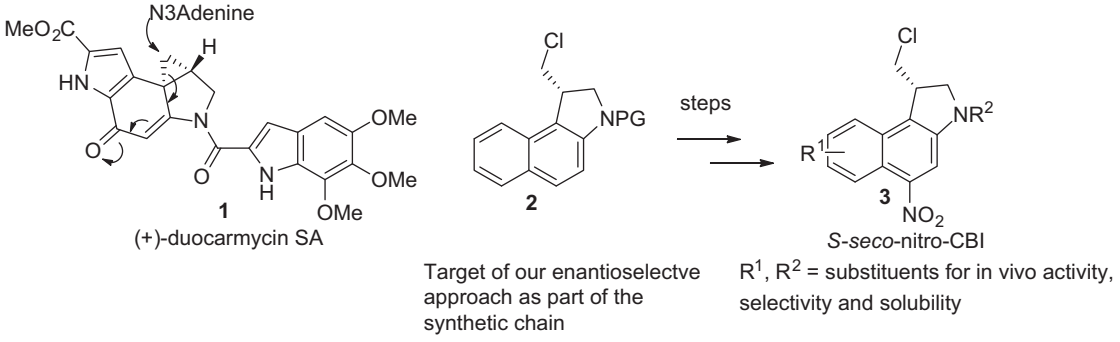


Figure 1. (+)-Duocarmycin SA (**1**) and the nitroCBI prodrugs (**2**/**3**) derived from the natural product.

* Corresponding author. Tel.: +64 9 373 7599; fax: +64 9 373 7502.
E-mail address: d.heinrich@auckland.ac.nz (D.M. Heinrich).

0040-4039/$ - see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2011.10.105

mour blood vessel networks often observed in cancer tissue.[11–13] This makes hypoxia a target for selective cancer treatment, using non-toxic prodrugs that can be activated in hypoxic cells,[10,14] releasing the active drug which then leads to apoptosis of the cancer cell.[15] Our group previously developed the nitro *seco*-1,2,9,9a-tetrahydrocyclopropa[*c*]benz[*e*]indol-4-ones (nitroCBIs)/aminoCBI *seco*-prodrug concept with hypoxia as the target.[14] The non-alkylating *seco*-nitroCBI prodrug is activated in hypoxic cells by a multiple-step reduction of the nitro group to the corresponding amine which then undergoes rapid spirocyclisation to the DNA-alkylating active form.[16] The selectivity arises because of the reversibility of the first one-electron reduction step, which is reversed rapidly by oxygen in normal well-perfused cells.

The potency of the duocarmycins and related aminoCBIs can be modulated by different means. Substituents on the naphthoindoline subunit modulate in vivo activity and DNA sequence selectivity.[17] The only chiral centre in the *seco*-prodrug plays an important role as well. The *R*-enantiomers of the alkylating subunit of both the natural products and known derivatives are considerably less potent than the *S*-enantiomers.[18] The sequence selectivity of DNA alkylation is also influenced by the chiral centre.[19]

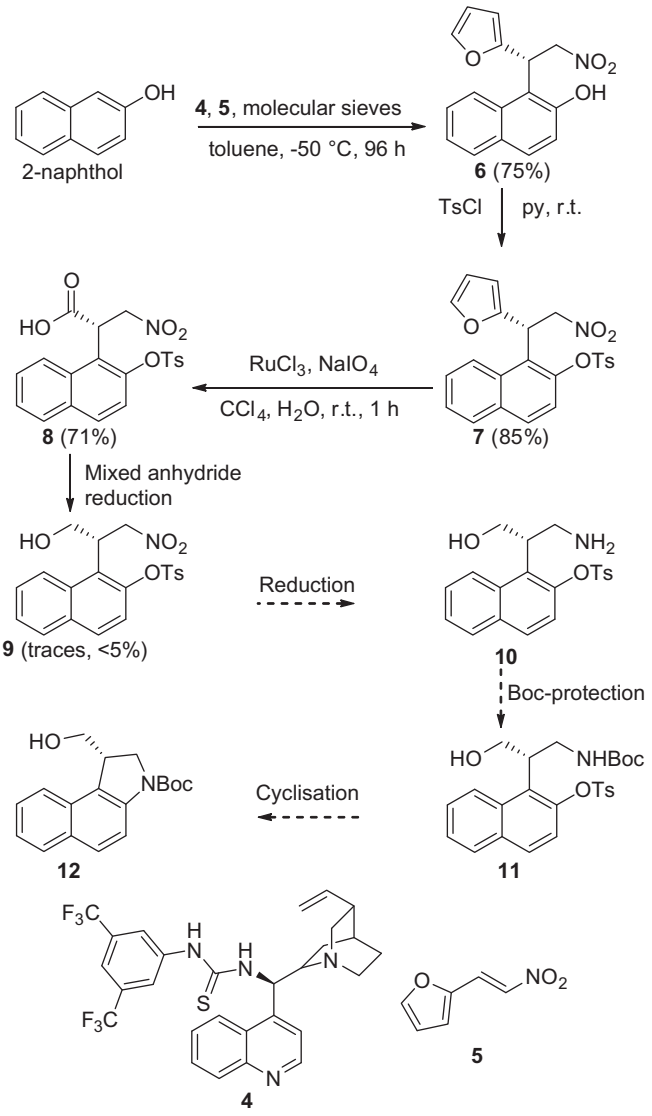
The significant variation in potency of the enantiomers has led to several endeavours aimed at the enantioselective synthesis of the DNA-alkylating subunit,[20] in order to produce only the desired *S*-enantiomer. The known synthetic approaches to the *S*-enantiomer all target 1,2,9,9a-tetrahydrocyclopropa[*c*]benz[*e*]indol-4-one (CBI) as the alkylating subunit.[2,21] The prodrug concept is realised by attaching a cleavable protecting group to the hydroxy moiety at the 6-position of the indole,[9,22] causing the drug to become inert. Once the prodrug is inside the cancer cell, the protecting group is cleaved through a mechanism specific for the cancer cell, for example a galactosidase cleaves the attached galactose and therefore releases the drug.[23]

However, in the nitro-CBI approach, the 5-position of the indoline needs to be left unoccupied in order to introduce the nitro group into the aromatic cycle later in the synthetic pathway.[14] This means the aromatic moiety of the indoline of nitroCBI precursors has electronic properties that differ from the derivatives previously published and that have been utilised successfully in enantioselective approaches. Thus several of the above synthetic pathways did not work for the nitro-CBIs,[9,24,25] suggesting the need for a new enantioselective approach.

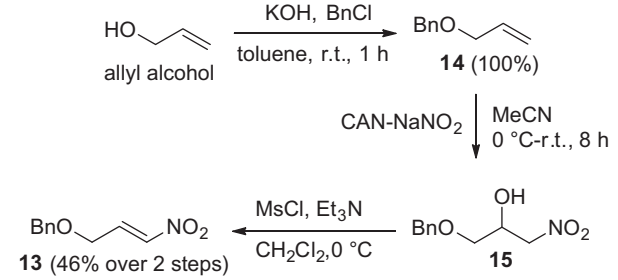
This project aimed at synthesising indoline **2** which can be converted by known methods into **3** (Fig. 1) which is part of the synthetic sequence previously reported by us for the racemic synthesis of nitro-CBIs.[26]

Our first approach was based on the work of Chen and co-workers who showed that naphthol could be alkylated enantioselectively via a Friedel–Crafts alkylation, promoted by a chiral thiourea catalyst.[27] The stereochemistry was assigned by derivatization of the product as a crystalline intermediate and X-ray analysis of the derived crystals.

For our means, catalyst **4** and nitro olefin **5** (Scheme 1) were the most useful. We anticipated that alkylation product **6** could be oxidized, after protecting the hydroxy group (**7**), to the corresponding acid **8**. Reduction of acid **8** would give the alcohol **9**. Reduction of the nitro group and Boc-protection of the resulting amine **10** would provide precursor **11** which might be suitable for cyclisation to give the desired indoline building block **12**. Cyclisation of the precursor **11** to the desired indoline **12** could be achieved under various conditions. However, to date, only a few examples have been reported where intramolecular cyclisation between a sulfonamide and an aryl triflate leads successfully to an indoline,[28–30] while the intramolecular cyclisation of carbamates (such as the Boc-protected amine **11**) is only known for aryl halide examples.[31]



Scheme 1. Initial strategy for the synthesis of indoline **10**.



Scheme 2. Synthesis of nitro olefin **13**.

According to the literature protocol we synthesized chiral (*S*)-1-[1-(furan-2-yl)-2-nitroethyl]naphthalen-2-ol (**6**) in 75% yield and 90% ee. The Friedel–Crafts product was then converted into the *p*-toluenesulfonate **7** in 85% yield. Oxidation with $RuCl_3/NaIO_4$ provided the acid **8** in 71% yield. The corresponding alcohol **9** was obtained by reduction of the free acid. Reduction to alcohol **9** was initially attempted using $LiAlH_4$ and $BH_3{\cdot}Et_2O$ complex, which in the case of $LiAlH_4$ led to decomposition of the starting material,