Bioorganic & Medicinal Chemistry Letters 23 (2013) 5066–5069

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

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

A synthetic approach to novel carvotacetone and antheminone analogues with anti-tumour activity

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ARTICLE INFO

Article history:
Received 31 October 2012
Revised 16 July 2013
Accepted 17 July 2013
Available online 26 July 2013

Keywords:
Anti-cancer
Natural product
Quinic acid
Synthetic analogue

ABSTRACT

A synthetic approach to analogues of the terpenoid natural product antheminone A is described which employs (−)-quinic acid as starting material. A key conjugate addition step proved to be unpredictable regarding its stereochemical outcome however the route allowed access to two diastereoisomeric series of compounds. The results of biological assay of the toxicity of the target compounds towards non-small-cell lung cancer cell line A549 are reported.

The α-oxymethyl-α,β-cyclohexenone moiety is embedded in a number of bioactive natural products, including 2-crotonyloxymethyl-(4*R*,5*R*,6*R*)-4,5,6-trihydroxycyclohex-2-enone (COTC, **1**),[1] several carvotacetone derivatives (e.g. **2**)[2] and the terpenoid, antheminone A (**3**).[3] Of these, both **1** and **3** have been found to display high toxicity towards a variety of cancer cell lines[3,4] and this has prompted substantial scientific interest in compounds of this type (Fig. 1).

The focus of our recent research effort has been the preparation of analogues of **1**–**3** with general structure **4** which embodies five loci for diversification. Initial studies into the influence of degree of hydroxylation of the carbacyclic core on in vitro toxicity towards non-small-cell lung cancer cell lines (A549 and H460) have shown that mono-hydroxylation is optimal: thus, compounds **5** and **6** are the most potent reported by ourselves to-date and, importantly, both compounds show notable toxicity towards cancer cell lines from a variety of tissue types (Fig. 2).[5]

Prompted by these findings, our interest has focussed on the development of synthetic approaches towards mono-hydroxylated compounds related to **2** and **3** which bear a C-linked substituent at C5. Herein we describe an approach to compounds of this type which employs (−)-quinic acid (**7**) as starting material together with the results of bioassay of four target compounds against the cancer cell line A549.

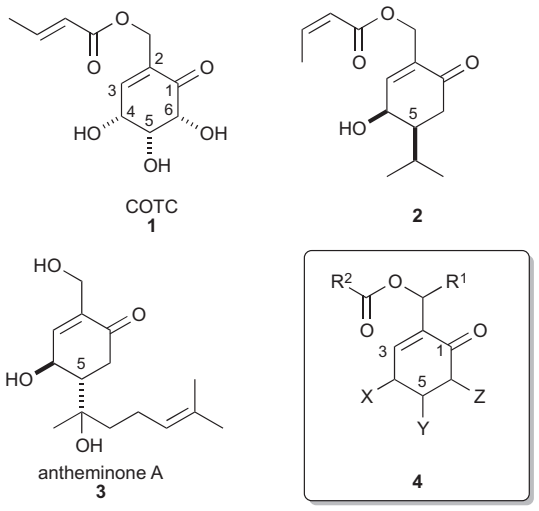

Figure 1. Structures of α-oxyalkyl-α,β-cyclohexenones.

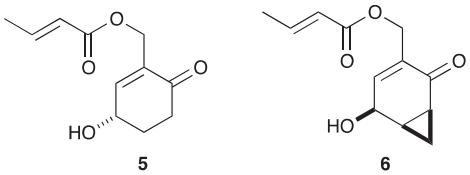

Figure 2. Previously synthesised analogues of COTC with anti-tumour activity.

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http://dx.doi.org/10.1016/j.bmcl.2013.07.041

The pivotal intermediate in our approach to the target compounds was γ-oxygenated cyclohexenone **8** which was prepared in 4 steps and 79% overall yield from (−)-quinic acid (**7**) using the conditions reported previously by ourselves (Scheme 1).[5d]

Conjugate addition to **8** may occur either *syn* or *anti* to the C4-substituent to give ***syn*-9** or ***anti*-9**, respectively: despite a number of relevant investigations over the years, a reliable model for predicting the stereochemical outcome of transformations such as this remains illusive. This is exemplified by a report by Corey[6] which describes the outcome of investigations of the reaction of spirocyclic enone **10** with lithiumdialkyl cuprates—in which a preference was observed for conjugate addition *syn* to the oxygen substituent in the presence of TMSCl (to give ***syn*-11**) and a reversal in selectivity in the absence of the additive (to give ***anti*-11**). In contrast, Danishefsky[7] reported that addition of lithiumdimethyl cuprate in the presence of TMSCl to γ-oxygenated cyclohexenone **12** gave solely the *anti* adduct **13** (Fig. 3).

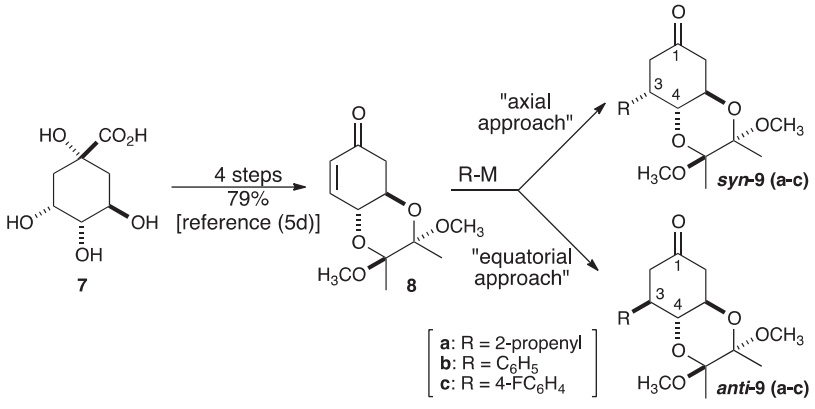
The rigid '*trans*-decalin' nature of **8** results in there being little steric differentiation between the two faces of the enone moiety and the C4-oxygen substituent, which is *pseudo*-equatorially disposed, would be expected to have negligible stereoelectronic influence on diastereofacial selectivity. It was our conjecture, therefore, that conjugate addition to **8** would proceed via an 'axial' trajectory to give ***syn*-9**.[8] Unfortunately, however, the stereochemical outcome of reactions of **8** with a range of Gilman cuprates proved to be wholly unpredictable as illustrated by the results in Table 1. Thus, under standard conditions, addition of di-(2-propenyl)-cuprate proceeded with reasonable facial selectivity to give ***anti*-9a**: the product ratio was unaffected by the presence of TMSCl however it was notably increased at low temperature. Contrarily, diphenylcuprate, in the presence of TMSCl, furnished the *syn*-isomer in excess at 0 °C, however, at room temperature ***anti*-9b** becomes the major product isomer. Di-(4-fluorophenyl)-cuprate displayed a similar preference for formation of the *syn*-isomer (***syn*-9c**) at 0 °C, however there was no discernible facial discrimination at room temperature.

Despite the unpredictable nature of these reactions, preparative quantities of all principal adducts could be obtained by fractional crystallisation (chromatographic separation of diastereoisomers was unsuccessful). In the first instance, stereochemical assignment of the adducts was based on examination of the respective vicinal coupling constants for C(4)H (e.g. ***syn*-9b**: $^3J_{3,4}$ = 5.1; $^3J_{4,5}$ = 10.4: ***anti*-9b**: $^3J_{3,4}$ = 11.0: $^3J_{4,5}$ = 9.5). The assignment was supported by the observation of nOe enhancements between C(5)H and C(3)H for ***anti*-9b** and between C(5)H and the aromatic CH's of ***syn*-9b**. Ultimately, structural confirmation was possible by X-ray analysis of crystalline samples of the two isomeric adducts (Fig. 4).[9,10]

Our preferred approach to the preparation of the target compounds is illustrated in Scheme 2 for the synthesis of phenyl-substituted compound **17**. Thus, eliminative removal of the BDA protecting group of ***anti*-9b** proceeded effectively in aqueous medium and in the presence of a catalytic amount of a Bronsted acid surfactant catalyst (dodecylbenzenesulphonic acid) to give **14**.[11] Subsequent protection of the liberated hydroxyl group as its triethylsilyl (TES) ether proceeded cleanly at low temperature to give **15** in a reproducible 48% yield over the two steps from **9b**. Following extensive investigations of a variety of reaction conditions, it was found that introduction of a hydroxymethyl group at C2 of **15** could be accomplished quite efficiently, and in a relatively short time, using Williams' surfactant-based procedure for the Morita–Baylis–Hillman (M–B–H) reaction.[12] Finally, the target compound **17**, which possesses a crotonate ester side-chain similar to that in COTC (**1**), was prepared by esterification of the primary hydroxyl of **16** followed by acid-mediated removal of the silyl protecting group.

Both the diastereoisomeric phenyl-substituted compound **18** and the 2-propylcompound **19**[13] were prepared in a similar manner to **17** whereas diol **20** was obtained by hydrolytic deprotection of the 2-propyl-substituted analogue of M–B–H adduct **16** (Fig. 5).

The four analogues **17**-**20** were assessed for their in vitro toxicity towards the non-small-cell lung cancer cell line A549. The assays were carried out by exposing cells to varying concentrations of each compound for 4 days and the number of surviving cells



Scheme 1.

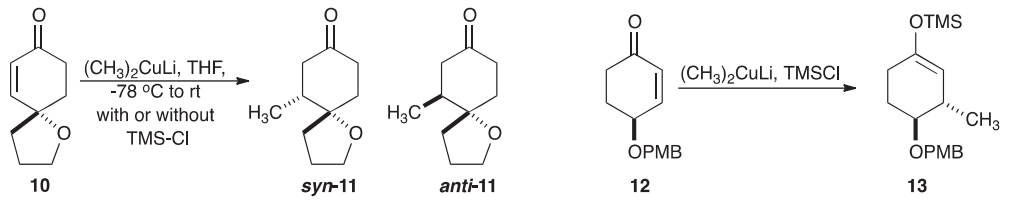


Figure 3. Conjugate addition reactions of organo-cuprates to γ-oxygenated cyclohexenones.