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Synthesis of the northern fragment of an epothilone D analogue from (−)-carvone

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ABSTRACT

A simple and effective synthesis of the chiral thiazole-containing fragment of an epothilone D analogue from (−)-carvone is described.

1. Introduction

Among microtubule stabilizing natural products (taxol, discodermolide, dictyostatin),[1–4] the epothilones (Epo)[5] are one of the most perspective candidates for a new antitumour agents. Six Epo derivatives are now at various stages of clinical assay,[6] including the Epo B lactam analogue ixabepilone,[7] which received FDA approval for the treatment of patients with locally advanced or metastatic breast cancer in 2007. The main shortcomings of the natural Epo for practical application are poor metabolic and chemical stability, toxicity and lipophilicity. The poor metabolic stability of Epo is expressed in a rapid in vivo lactone ring hydrolysis, the chemical instability is due to the epoxide-containing side chain (nucleophilic ring opening) and the 'southern' β-hydroxy ester fragment (dehydratation reactions and possible allylic ester transformations).

Accordingly, we concentrated on the synthesis of a novel Epo D lactam analogue **3**, in which the epoxide functional group is absent (toxicity reduction) and the methylene unit is isosterically displaced in the C^{15}–C^{3} fragment (chemical stabilization). Danishefsky and co-workers previously reported the synthesis of 12,13-desoxy analogue of **1**[8] and a lactam analogue **2**, which exhibited increased microtubulin stabilizing and advanced anticancer activity in comparison with natural Epo B **1**. Therefore, a new Epo derivative **3** is also of interest to SAR assay development.[9] This paper describes the synthesis of the thiazole-containing fragment **4** from the inexpensive natural terpene (−)-carvone **5** Scheme 1.

2. Results and discussion

(−)-Carvone is considered as a very convenient chiral starting compound for the synthesis of **4**. It has a trisubstituted *cis*-double bond, the correct stereochemistry at the chiral centre, the isopropylidene moiety as a methyl ketone equivalent and the keto group suitable for the chemoselective oxidative cleavage.

To transform (−)-carvone into α-hydroxy ketones **10a**,**b** suitable for the oxidative ring cleavage, Rubottom methodology was used (transformation of a ketone into an α-hydroxy ketone via silyl enol ether formation, followed by epoxidation and rearrangement).[10] α-Hydroxylation of ketones of the carvone series was reported previously.[11] The acetonide **7**, derived from epoxide **6**[12] was converted into TMS-enol ester **8** followed by m-CPBA oxidation, which yielded the TMS-protected α-hydroxy ketone **9**. Deprotection of the TMS–ether gave a mixture of isomeric hydroxy ketones **10a** and **10b** in a ratio of 10:1 (epimers at the hydroxyl-carrying centre). At the same time, the diastereomeric ratio (3:2) established during the formation of epoxide **6** was found to be unchanged by ^{13}C NMR spectroscopic analysis Scheme 2.

The mixture of **10a** and **10b** was then subjected to oxidative cleavage by the action of lead tetraacetate[13] in MeOH/C_6H_6 and the crude product was reduced using Luche conditions[14] ($NaBH_4$–$CeCl_3$). This reaction sequence gave the acetonide ester **12** in a good yield (88%). Acetonide ester deprotection followed by oxidative cleavage according to the procedure described above produced β-hydroxy ketone **14** Scheme 3.

The thiazole-containing phosphonium and phosphonate reagents **15a**–**c** were tested in the Wittig olefination reaction of

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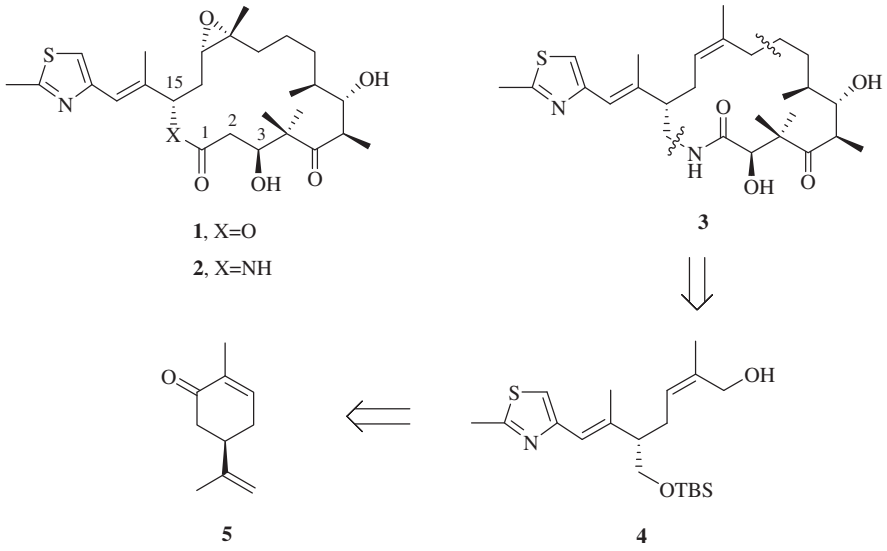


Scheme 1. Retrosynthetic analysis of the nothern fragment of the Epo D analogue **4**.

hydroxy ketone **14**. It was found that ylides **15a** and **15b** had low activity in the olefination reaction while **15c** smoothly reacted with ketone **14** producing the (*E*)-olefin[15] **16** in high yield. Subsequent hydroxyl protection and DIBAL-H reduction reactions afforded the target alcohol **4** Scheme 4 Table 1.

3. Conclusion

We have developed a synthesis of an Epo D analogue fragment from the known (−)-carvone. The prepared fragment will be used for the total synthesis of a novel Epo D analogue in our future investigations.

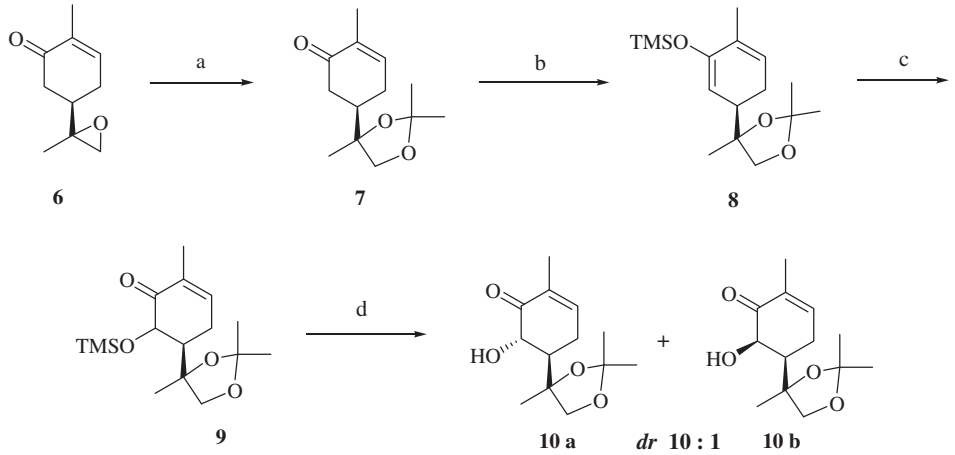
4. Experimental

4.1. General

Solvents were purified and dried before used by standard procedures. Reagents were generally the best quality commercial grade and used without further purification unless otherwise indicated. All reactions were carried in oven-dried glassware. TLC was performed using Sorbfil STC-1A 110 μm layer, silica gel 5–17 precoated foil plates. Column chromatography was carried out using 210–280 mesh silica gel. Optical rotations were measured using the sodium D line at 589 nm on a Perkin Elmer, Model 241 MC polarimeter. IR (infrared spectra) was recorded on a Shimadzu IRPrestige-21 spectrometer as a Nujol mull or as neat thin films on KBr plates. ^{1}H and ^{13}C NMR spectra were obtained using a Bruker AM-300 (300 MHz for ^{1}H and 75.47 MHz for ^{13}C) as solutions in $CDCl_3$ (Aldrich Chemical Company; spectra grade). Mass spectra were recorded on Shimadzu LCMS QP-2010EV (APCI) spectrometer. Elemental analyses were carried on a Euro EA 3000 CHNS-analyzer.

4.2. (5*R*,4′*RS*)-2-Methyl-5-(2′,2′4′-trimethyl-1′,3′-dioxolan-4′-yl)cyclohex-2-en-1-one (7)

To a stirred solution of **6**[12] (7.00 g, 42.2 mmol) in dry acetone (60 mL) was added $BF_3 \cdot Et_2O$ (9.53 g, 84.3 mmol) under Ar at room



a) $BF_3 \cdot OEt_2$, Me_2CO, rt, 1 h, 93%; b) LDA, TMSCl, THF, - 78 °C, 1 h, quant.; c) m-CPBA, 1 M aq. $NaHCO_3$, CH_2Cl_2, 10 °C, 2 h, 93%; d) TBAF, THF, 0-10 °C, 20 min, 83%.

Scheme 2. Synthesis of hydroxy ketones **10a**,**b** via the Rubottom reaction.