Tetrahedron Letters xxx (2015) xxx–xxx

Contents lists available at ScienceDirect

Tetrahedron Letters

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

Synthesis of (±) debenzoyl analogs of norsampsones as potential anticancer agents

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ARTICLE INFO

Article history:
Received 17 June 2015
Revised 16 July 2015
Accepted 17 July 2015
Available online xxxx

Keywords:
Acylphloroglucinols
Debenzoyl
Norsampsones
Anticancer

ABSTRACT

Synthesis of (±) debenzoyl analogs of norsampsones **1** and **2** is reported starting from commercially available 1,3-cyclohexadione in six steps with overall yields of 37% and 36%, respectively. Compounds **1** and **2** were tested for their anticancer activity and showed moderate anticancer activity against HeLa cell lines.

The polycyclic polyprenylated acylphloroglucinols (PPAPs) constitute a family of natural products whose antiseptic, antidepressant, and antibiotic properties have been known for centuries.[1–7] *Hypericum sampsonii* belongs to the Clusiaceae family which exhibits anticancer activity and has been used as a promising anticancer herb in Taiwan.[8] Very recently, Tian and co-workers[9] isolated norsampsones A–D (Fig. 1), four new dicarbonyl polyprenylated acylphloroglucinols from the plant *H. sampsonii*. They have reported structural elucidation, *plausible* biogenetic pathway, and biological evaluation of norsampsones A–D. We herewith report the synthesis of the (±) debenzoyl analogs of norsampsones. These analogs were tested for their anticancer activity against HeLa cell lines using MTT assay and were found to have moderate cell growth inhibitory activity.

We envisioned the synthesis of compounds **1** and **2** as shown in Scheme 1. Compounds **1** and **2** could be obtained by 1,4-addition of methyl nucleophile on intermediates **15** and **16**, respectively. Intermediates **15** and **16** could be afforded from dialkylation of synthon **5**, which in turn could be obtained from commercially available 1,3-cyclohexadione **3**.

1,3-Cyclohexadione was used as a starting material for synthesis of (±) debenzoyl analogs of norsampsones. 1,3-Cyclohexadione **3** was treated with iodine in methanol to afford the vinyl ether **4** in 92% yield (Scheme 2). Stork–Danheiser reaction of **4**, afforded the prenylated enone **5** in 89% yield as reported by Shibasaki et al. and spectral data matched with those in the literature.[10] Alkylation of enone **5** with LDA and prenyl bromide afforded compound **6** (*trans*/*cis* = 9:1) as reported by Ahmad et al.[11] The major *trans*-isomer of compound **6** was separated from *cis*-isomer and the ^{1}H and ^{13}C NMR spectra were found identical with those of the reported.[11] Similarly, enone **5** when treated with geranyl bromide provided the geranylated product **7** (*trans*/*cis* = 9:1) in 80% yield. The major *trans*-isomer of compound **7** was separated by column chromatography with 80% yield and its identity was confirmed by ^{1}H, ^{13}C NMR, and HRMS data.

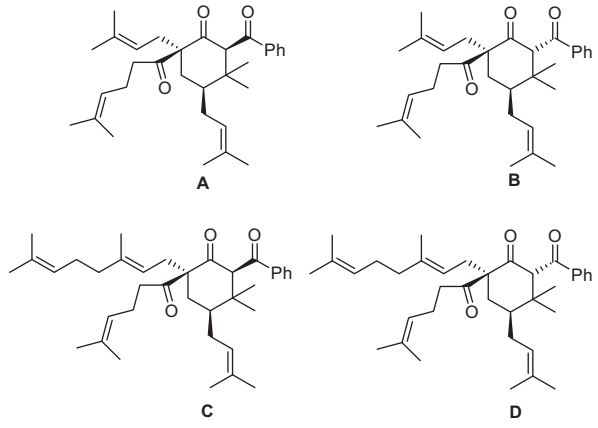

Figure 1. Structures of norsampsones A–D.

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http://dx.doi.org/10.1016/j.tetlet.2015.07.057
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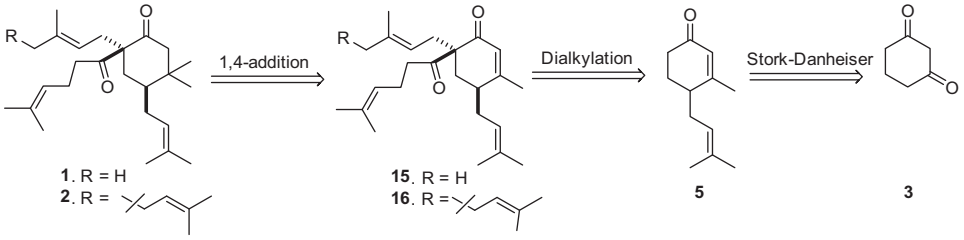
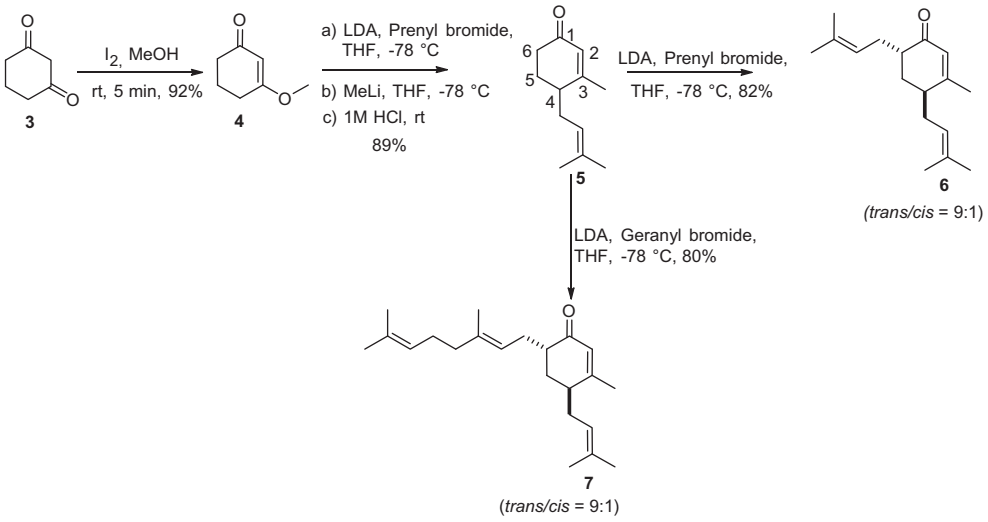
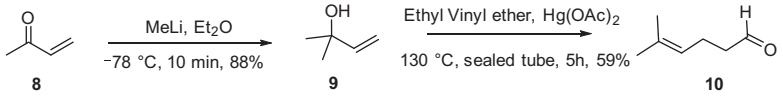


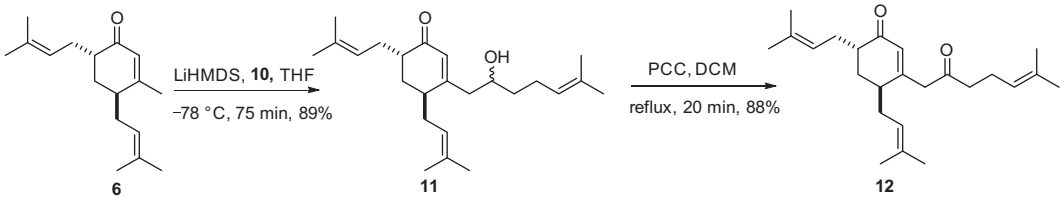
Scheme 1. Retrosynthesis of debenzoyl analogs **1** and **2** of norsampsone.



Scheme 2. Synthesis of compounds **6** and **7**.



Scheme 3. Synthesis of aldehyde **10**.



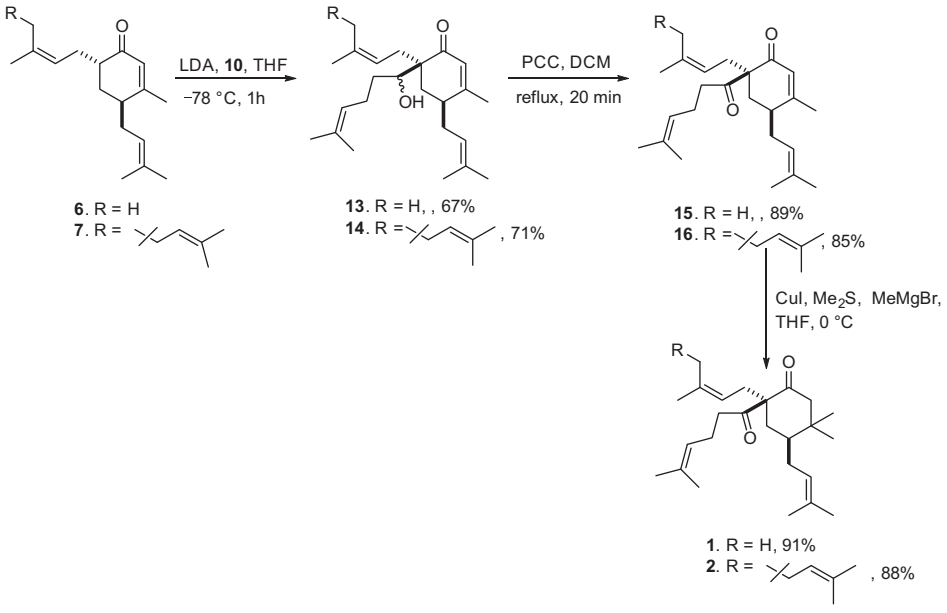
Scheme 4. Synthesis of **12**.

2-Methylbut-3-en-2-ol **9** was prepared from methyl vinyl ketone **8** by 1,2-addition of MeLi in dry ether at −78 °C for 10 min. Compound **9** was then treated with ethyl vinyl ether in the presence of catalytic $Hg(OAc)_2$ in a sealed tube at 130 °C for 5 h to obtain a rather volatile γ,δ-unsaturated aldehyde **10** in 59% yield by the aliphatic Claisen rearrangement (Scheme 3).

In an attempt to introduce the C6-side chain, compound **6** was alkylated with aldehyde **10** using LiHMDS to generate the enolate to give compound **11** as a diastereomeric mixture (Scheme 4). Since, we generated a mixture of diastereomers, we wanted to simplify the analysis and hence oxidized the mixture of alcohols to ketone **12** in 88% yield. ^{1}H, ^{13}C NMR and HRMS data confirmed the formation of ketone **12**.

Compounds **6** and **7** on reacting with aldehyde **10** in the presence of LDA at −78 °C afforded alcohol **13** and alcohol **14** in a diastereomeric ratio of 9:1 and 7:3, respectively (Scheme 5). The diastereomeric ratio was confirmed from ^{1}H NMR spectra. Without separating the diastereomers of compounds **13** and **14**, oxidation of **13** and **14** with PCC afforded compounds **15** and **16**, respectively in good yields (89% and 85%). Conjugate addition of the organocuprate derived from methylmagnesium bromide and CuBr to enone **15** and **16** in THF at 0 °C afforded (±) debenzoyl analogs of norsampsones **1** and **2**, respectively, in excellent yields. The structures were confirmed using NMR and HRMS data. Thus, we have reported synthesis of compounds **1** and **2** with overall yields of 37% and 36%, respectively.[12] On the basis of these results,

Please cite this article in press as: Jadhav, A. R.; et al. *Tetrahedron Lett.* (2015), http://dx.doi.org/10.1016/j.tetlet.2015.07.057



Scheme 5. Synthesis of **1** and **2**.

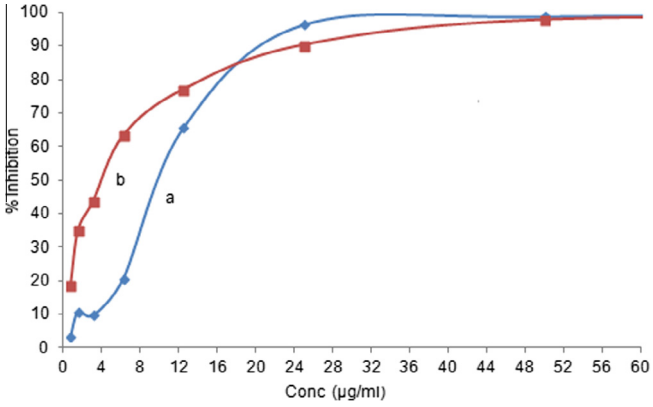


Figure 2. MTT assay results for (a) compound **1** and (b) compound **2**.

catalytic asymmetric synthesis of norsampsones using Koga alkylation[13] and studies of its biological activities are currently ongoing.

Since norsampsones C, showed anticancer activity (IC_{50} >20 μM) we thought to screen the synthesized compounds **1** and **2** for their anticancer activity using MTT assay against HeLa cell lines. Compounds **1** and **2** exhibited moderate antiproliferative efficacy for cancer cells. As illustrated in Figure 2, IC_{50} values for the compounds **1** and **2** were 19 and 7 μM, respectively, that prove the anti cancer potential of compounds **1** and **2** and open a way for future therapeutic applications of these compounds in cancer treatment.

In summary a simple, flexible, and highly efficient synthetic approach for the synthesis of (±) debenzoyl analogs of norsampsones **1** and **2** has been developed. The overall yields of **1** and **2** was found to be 37% and 36%, respectively, over six steps. Compounds **1** and **2** exhibited promising anticancer activity against HeLa cell lines.

Acknowledgments

V.H.J. thanks DST, New Delhi for the INSPIRE Faculty Award (IFA 12, CH-44) and Fast Track Grant (CS-041/2013). V.H.J. also thanks the Director, NCL for providing all the infra-structural facilities.

Supplementary data

Supplementary data (detailed experimental procedure, characterization of the products and copies of spectra are provided) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2015.07.057.

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