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Fragmentations of 13-oxo-taxyunnansin A and their application to preparation of *abeo*-paclitaxel and *abeo*-docetaxel analogues

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ABSTRACT

Two interesting unprecedented fragmentations of 13-oxo-taxyunnansin A (**3**), initiated by treatment with ^{t}BuOK and Red-Al, respectively, have been discovered, optimized and successfully applied to the synthesis of novel *abeo*-paclitaxel and *abeo*-docetaxel derivatives. Eight new derivatives of *abeo*-paclitaxel and *abeo*-docetaxel possessing the structurally simplified 11 (15→1)-*abeo*-taxane skeleton with an oxetane ring and π bond conjugate system were accordingly prepared for the further evaluation of anticancer activities.

Natural products are an abundant source of diverse bioactive metabolites. Chemical study on various natural products has provided the impetus to great advances in organic chemistry, and led to new discovery of diverse natural scaffolds, as well as huge number of variously modified natural products with greater synthetic accessibility or improved bioactivity.[1] Paclitaxel (Fig. 1, **1a**) is a unique diterpenoid first isolated by Wall and Wani from *Taxus brevifolia* Nutt.[2] Paclitaxel and its semisynthetic analogue docetaxel (**1b**) have proved to be the most important anticancer drugs today because of their clinical effectiveness and novel mechanism of action.[3] Since the discovery of paclitaxel, intense chemical studies on constituents of different yew trees have resulted in the isolation and identification of approximately 400 taxoids.[4] Among these, the most frequently found core structure is the pentamethyl [9.3.1.0] tricyclopentadecane skeleton, which is now often called the normal taxane skeleton. The chemistry and bioactivity of this type of taxoids have been thoroughly investigated.[1b]

In recent years, another type of taxoids with 11(15→1)-*abeo*-taxane skeleton have also been found in increasing numbers, and have become the second largest category of taxoids. However, only very limited chemical properties have been disclosed of these 11(15→1)-*abeo*-taxoids. Simple modifications have been reported, such as introduction of acetyl, troc, *N*-benzoyl-(2′*R*,3′*S*)-3′-phenyl isoserine, and TES groups into the existing functional groups at C-5, C-13 position(s).[5] In addition, a small number of 11(15→1)-*abeo*-paclitaxel analogues were also prepared via direct rearrangement from the known paclitaxel analogues.[6] Because of potential biological and pharmaceutical importance of *abeo*-paclitaxel derivatives, it still calls for new contents in the development of novel modification methods and preparation of new *abeo*-taxoid analogues possessing unique scaffolds for the corresponding biological and pharmaceutical applications.

Taxyunnansin A (Fig. 1,**2**), which was firstly isolated from *Taxus wallichiana* in 1993,[7] possesses the 11(15→1)-*abeo*-taxane skeleton with an oxetane ring. To the best of our knowledge, no chemical and biological studies on **2** have been reported yet. In the course of our phytochemical study on the branches and leaves of *Tsuga chinensis*, a considerable amount of taxyunnansin A

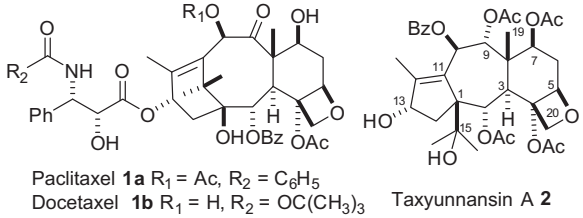

Figure 1. Paclitaxel, doctaxel and taxyunnansin A.

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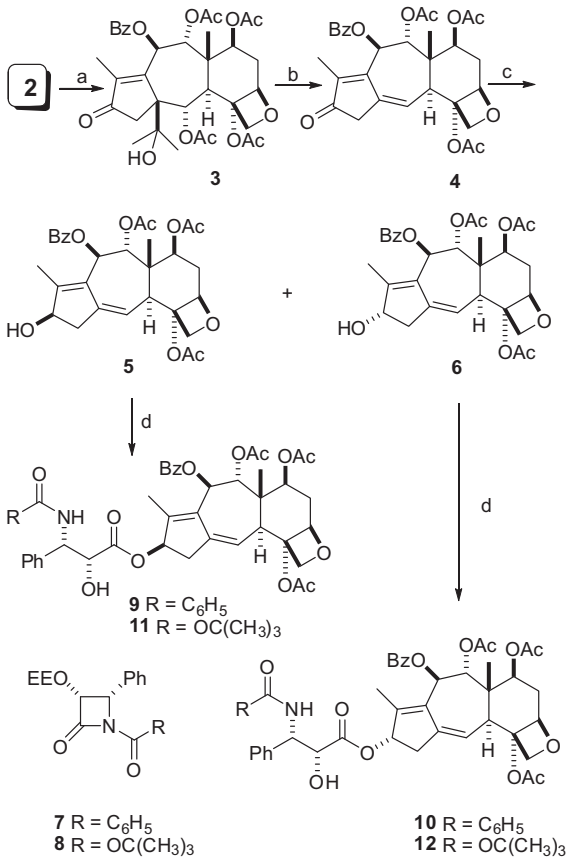
(**2**, approximately 20 g) has been accumulated. This provided us with a rare opportunity to launch our study on the modification of 11(15→1)-*abeo*-taxoids.

Starting from the natural material **2**, development of new derivatives with reduced structural complexity (compared to the parent natural product) was attempted. After persistent screening of chemical transformations of **2**, it was found that treatment of 13-oxo-taxyunnansin A (**3**) with ^{t}BuOK and Red-Al, respectively, led to three interesting compounds **4** (Scheme 1), **13** and **14** (Scheme 2) in good or reasonable yields. More interestingly, these three products via eliminative fragmentation of **2** represent a novel simplified structure type in this category of taxoids. With our knowledge in taxoids, these compounds could be very unique precursors for a series of new potentially useful derivatives of *abeo*-paclitaxel and *abeo*-docetaxel by the simple conjugation with β-phenylisoserine side chain. In this Letter, we wish to report our interesting findings in the preparation of new *abeo*-paclitaxel and *abeo*-docetaxel derivatives. These results are believed to be a new addition to the few literatures on the chemistry of *abeo*-taxoids.

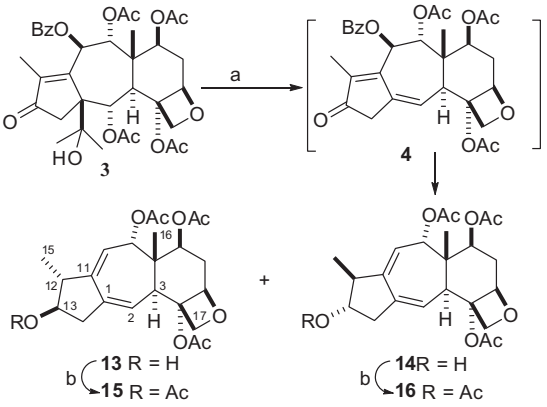
13-Oxo-taxyunnansin A (**3**), the common precursor in this work, was prepared by an efficient PDC oxidation of the C-13 hydroxyl of **2** (quantitative yield, Scheme 1). Treatment of **3** with ^{t}BuOK resulted in an interesting fragmentation. The isopropanol



Scheme 1. Reagents and conditions: (a) PDC, CH_2Cl_2, rt, 100%; (b) ^{t}BuOK, THF, rt, 77%; (c) $NaBH_4$, $CeCl_3$, MeOH, 0 °C, **5** (32%), **6** (54%); (d) (i) NaHMDS, **7** or **8**, THF, −78 °C; (ii) 0.5 N HCl, THF 0 °C to rt, **9** (30%), **10** (30%), **11** (26%), **12** (73%).

moiety at C-1 and the acetyl group at C-2 were eliminated during this process, giving a simpler conjugated dienone product **4** in 77% yield.

Because C-13 ketone of **4** could be further reduced, it would provide us an opportunity to introduce the β-phenylisoserine side



Scheme 2. Reagents and conditions: (a) Red-Al, THF, −40 °C, **13** (26%), **14** (23%); (b) Ac_2O, Pyr., DMAP, 1 h, 100%.

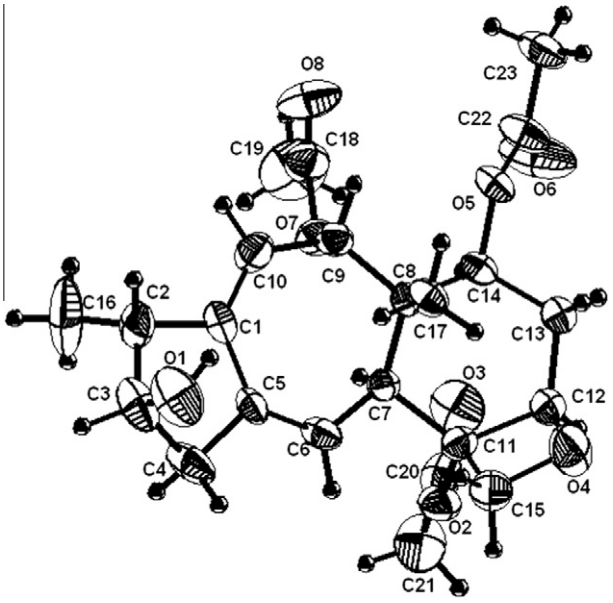


Figure 2. X-ray crystallographic structure of **13**.

chain. Following this idea, further reduction of the C-13 ketone with $NaBH_4$ and $CeCl_3$ was carried out, providing the C-13α and C-13β alcohols in 32% (**5**) and 54% (**6**) yields, respectively. In this reaction, lowering the reaction temperature or use of other reducing reagents could not improve the diastereoselectivity. It is supposed that the disappearance of β-oriented isopropanol moiety at C-1 might lead to the deprivation of substrate-controlled diastereoselectivity. It is noteworthy that all of our attempts failed in direct elimination of the isopropanol moiety at C-1 of the natural material **2** (without pre-treatment with PDC). This mentions that the C-13 ketone functionality is necessary for the above cascade eliminations, leading to a more stable conjugate system in product **4**. Parallel acylation of **5** and **6** with β-lactam **7**[8] afforded *abeo*-paclitaxel analogues **9** and **10**, respectively. Using β-lactam **8** as the acylating reagent, two additional *abeo*-docetaxel analogues **11** and **12** were prepared, respectively (Scheme 1). These four compounds **9**–**12**, embedded with a simplified unusual *abeo*-taxane skeleton with an oxetane ring and a 11:12,1:2-diene moiety, represent a novel class of new *abeo*-paclitaxle and *abeo*-docetaxel derivatives.

Another novel type of fragmentation was observed when 13-oxo-taxyunnansin A (**3**) was reduced with Red-Al. A previous report has shown that 13-oxo-7-TES-baccatin III could be

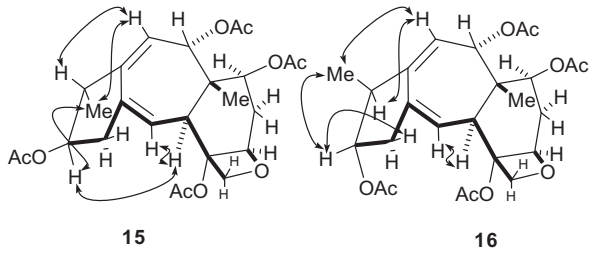
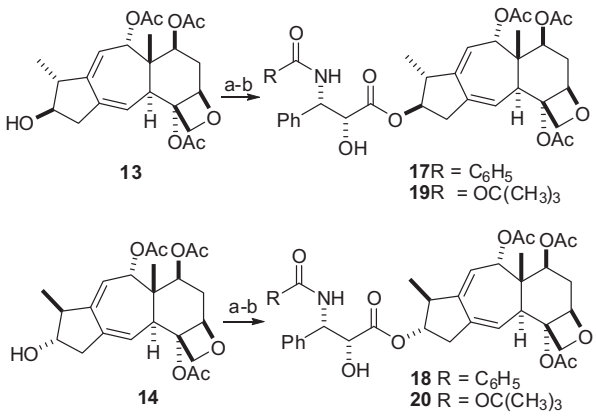


Figure 3. Selected ROESY correlations of **15** and **16**.



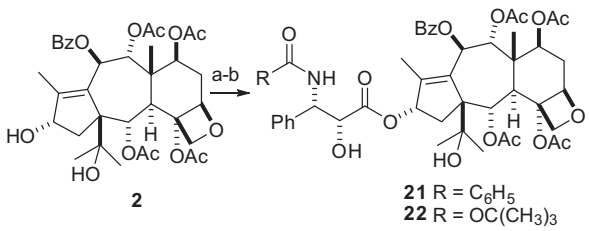
Scheme 3. Reagents and conditions: (a) NaHMDS, then **7** or **8**, THF, −78 °C; (b) 0.5 N HCl, THF 0 °C to rt; **17** (24%), **18** (28%), **19** (26%), **20** (40%).

selectively debenzoylated at the C-2 position using Red-Al as the hydride-transfer reagent.[9] In this case, a very fast sequential reaction was observed when the *abeo*-taxoid **3** was treated with Red-Al in THF at −40 °C. During this process, compound **4** was firstly generated and then completely converted into two new compounds **13** and **14** (Scheme 2). Lowing the reaction temperature to −78 °C made no difference to the results. The structure of **13** was determined by spectroscopic analyses and further confirmed by the single-crystal X-ray diffraction study (Fig. 2).[10]

After comparison of the ROESY spectrum of **13** and **14**, it was difficult to assign the relative configuration of C-13-OH and C-12-Me based on the ROESY spectrum of **14**. Treatment of compounds **13** and **14** with Ac_2O afforded compounds **15** and **16**, respectively (Scheme 2). Inspection of ROESY spectra of **15** and **16** showed that there was ROESY correlation between H-13 and H-3α in compound **15**, while such a correlation was not observed in **16**. Those results suggested that the H-13 in **13** and **15** were α-oriented and the H-13 in **14** and **16** were β-oriented. Furthermore, ROESY correlation between H-13β and H-15 was observed in compound **16**, and no ROESY correlation between H-13β and H-12 of **16** was detected. These indicated that the C-12-Me was β-oriented in compounds **14** and **16** (Fig. 3).

Using the similar procedures as those in Scheme 1, *abeo*-paclitaxel analogues **17** and **18**, and *abeo*-doctaxel analogues **19** and **20** were prepared from compounds **13** and **14**, respectively (Scheme 3). These four new derivatives **17**–**20** are characterized by a simplified *abeo*-taxane skeleton with an oxetane ring and a 1,3-conjugated diene in the seven-member ring.

For future comparison in the biological activity screening, we also prepared analogues **21** and **22** by direct introduction the β-phenylisoserine side chain to the starting material **2** (Scheme 4). Derivative **21** was previously reported by Liang's group and its cytotoxicity against KB cell line with an ED_{50} of 11.0 μg/mL.[6c]



Scheme 4. Reagents and conditions: (a) NaHMDS, **7** or **8**, THF, −78 °C; (b) 0.5 N HCl, THF 0 °C to rt, **21** (59%), **22** (29%).

In summary, chemical transformations of natural product taxyunnansin A (**2**) have been explored and two unique types of eliminative fragmentations have been discovered in this work. The products generated from these fragmentations were successfully applied to the synthesis of a series of new *abeo*-paclitaxel and *abeo*-docetaxel analogues **9**–**12** and **17**–**20**, which possess the simpler taxoids core structures. This study not only provides a new class of paclitaxel derivatives with novel structures, but also sheds a new light into the unique chemical behaviour of the 11(15→1)-*abeo*-taxoids. The interesting fragmentations found in this work could be further applied in other *abeo*-taxoids, and will therefore benefit those efforts to synthesizing biologically and pharmaceutically important taxoid derivatives.

Acknowledgements

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Supplementary data

Supplementary data (experimental details and full spectral data for new compounds) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.11.008.

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10. *Crystallographic data of compound* **13**: $C_{23}H_{30}O_8$, MW = 434.49; monoclinic, space group $P2_1$; a = 10.304 (1) Å, b = 10.498 (1) Å, c = 11.017 (1) Å, α = 90.00, β = 109.24 (1), γ = 90.00, V = 1125.2 (1) Å^3, Z = 2, d = 1.282 g/cm^3, crystal dimensions 0.05 × 0.10 × 0.30 mm was used for measurements on a MAC DIP-2030K diffractometer with a graphite monochromator ($\omega - 2\theta$ scans,

$2\theta_{max} = 50.0^{\circ}$), Mo K$\alpha$ radiation. The total number of independent reflections measured was 2455, of which 2422 were observed ($|F|^2 \geqslant 3\sigma|F|^2$). Final indices: $R_f = 0.0504$, $Rw = 0.1481$ ($w = 1/\sigma\ |F|^2$). The crystal structure of compound **13** was solved by direct method SHLXS-97 (Sheldrick, 1990) and expanded using the difference Fourier technique, refined by the programme SHLXL-97 (Sheldrick, 1997), and the full-matrix least-squares calculations. Crystallographic data for the structure of compound **13** have been deposited with the Cambridge Crystallographic Data Centre (deposition no. CCDC 791662). These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.