



Synthetic studies toward nortriterpenoids of *schisandraceae* family. Approach to the construction of functionalized C/D and A/B ring units of micrandilactone C and rubrifloradilactone B

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ARTICLE INFO

Article history:

Received 30 August 2011
Revised 20 September 2011
Accepted 22 September 2011
Available online 2 October 2011

Keywords:

Diels–Alder reaction
Metathesis
Terpenoids
Lactone

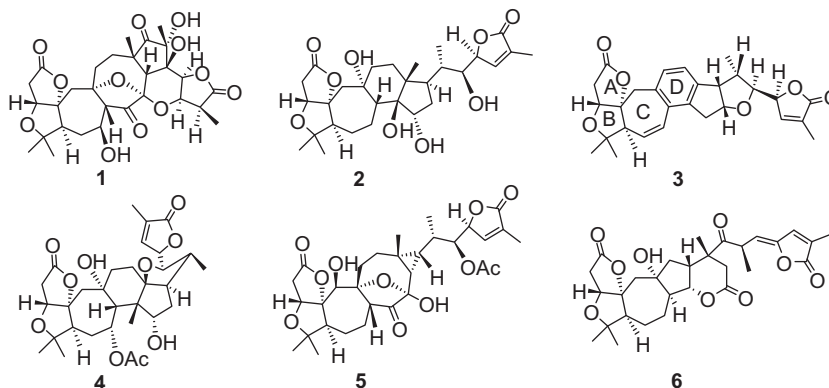
ABSTRACT

Construction of 6/7 fused bicycles featuring C/D rings of micrandilactone C and rubrifloradilactone B is reported through IMDA reaction of properly designed substrates. Also a route to the construction of a tricyclic having A/B ring of nortriterpenoids of *schisandra* family is reported using RCM and a bromonium ion initiated cycloetherification reaction as the key steps.

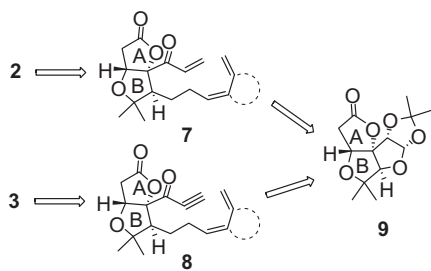
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Plants of the *Schisandraceae* family continue to be a rich source of highly bioactive nortriterpenoids.¹ Extracts of the leaves and bark of these plants are extensively used as folk medicines in China for thousands of years. Over the years a large number of compounds belonging to the family of triterpenoids with densely oxygenated novel polycyclic skeletons have been isolated from the plants of this family. Biosynthetically these compounds are proposed to be derived from cycloartane.

Depending on the structural pattern, they have been classified into six different types such as schisanartane (e.g. micrandilactone A **1**), schiartane (e.g. micrandilactone C **2**), 18-nor schiartane (e.g. rubrifloradilactone B **3**), 18 (13→14)-*abeo*-schiartane (wuweizidilactone C **4**), pre-schisanartane (e.g. pre-schisanartanin A **5**) and wuweiziartane (e.g. schinrilactone A **6**). Many of these compounds exhibit promising medicinal properties. For example, micrandilactone C **2**,² isolated from the leaves and



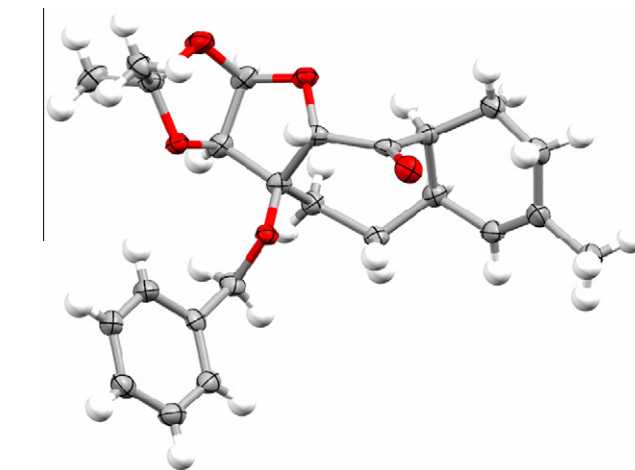
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Scheme 1. Retrosynthesis.

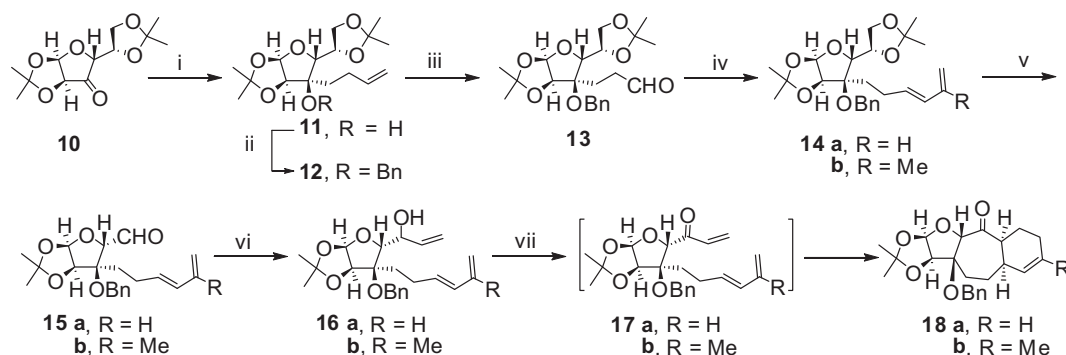
stems of *Schisandra micrantha*, possesses anti-HIV activity with an EC_{50} value of $7.71 \mu\text{g mL}^{-1}$. Rubrifloradilactone B **3**,³ isolated from the leaves and stems of *Schisandra Rubriflora*, exhibits anti-HIV activity with an EC_{50} value of $9.75 \mu\text{g mL}^{-1}$. The unique architectural features combined with the remarkable medicinal properties, *schisandra* terpenoids have elicited considerable interest⁴ among synthetic organic chemists. Examination of the structures reveals the presence of the A/B/C ring as the common structural unit. Thus synthetic efforts have so far remained restricted to the development of strategies for the construction of A/B^{4j,k,d} or A/B/C^{4b,g,l,n} fragments. There are also few reports on the construction of the central carbocyclic^{4a,e,f,h,i,m,o} core of some of these compounds. However there is no report aimed at the synthesis of micrandilactone C **2**, and there is only a single report⁵ on the construction of a tricyclic core structure of rubrifloradilactones.

Remarkable inhibitory activity of these two terpenoids against HIV-1 replication stimulated our interest in developing routes to the total synthesis of these natural products. We initially embarked on developing a flexible route that could be employed to construct functionalized tetracyclic A/B/C/D fragments present in both **2** and **3**. Retrosynthetically, an intramolecular Diels–Alder (IMDA) reaction in an appropriately designed substrate having the diene–dienophilic component stitched together through the pre-built A/B ring was envisaged as the key step (Scheme 1). To this end an IMDA reaction in **7** was considered for the construction of the C/D ring present in **2** while an IMDA reaction in **8** having a conjugated acetylenic ketone as the dienophilic component could be employed for the synthesis of the C/D ring aromatic analogue present in **3**. Precursors **7** and **8** could in principle be available from **9**. Herein we report the preliminary results of our investigation on IMDA reaction for the construction of C/D rings of **2** and **3** and a route to the synthesis of the projected intermediate **9** featuring A/B ring present in a large number of *schisandra* nortriterpenoids.

Figure 1. X-ray structure of compound **18b**.

We initially focussed on determining the feasibility of the IMDA reaction to construct 6/7 fused ring system as it is present in a large number of terpenes other than *schisandra* nortriterpenes. Intramolecular Diels–Alder reaction has been extensively explored to construct hydrindane and decalin systems. However, there are only few reports⁶ on IMDA reactions of undecatrienones to produce 6/7 fused bicycles due to their significantly reduced reactivity toward cycloaddition. Successful construction of 6/7 fused rings⁷ by IMDA reaction requires high temperature,^{7a–c} long reaction time^{7d} and even in some cases high pressure.⁸ During this investigation we observed that intramolecular Diels–Alder reaction of the undecatrienones **17** and **20** in which the dienes and the dienophiles were tethered through a furanosugar unit is very facile.

The precursor **17a** for the IMDA reaction was prepared as delineated in Scheme 2. Reaction of the glucose derivative **10** with the Grignard reagent prepared from 4-bromo-1-butene led to the known carbinol **11**⁹ in 50% isolable yield. Protection of the hydroxyl group as benzyl ether **12** followed by cleavage of the terminal alkene unit produced the aldehyde **13** in over all excellent yield. The aldehyde **13**¹⁰ was then subjected to Wittig reaction with the ylide generated from allyl triphenylphosphonium bromide to produce the diene **14a** in good yield. Selective deprotection of the 5,6-acetonide moiety followed by periodate cleavage of the resulting vicinal diol provided the aldehyde **15a**. Addition of vinyl magnesium bromide to the aldehyde **15a** produced the carbinol **16a**. When the carbinol **16a** was subjected to Dess–Martin periodinane (DMP) oxidation at rt, to our delight the tricyclic ketone **18a**



Scheme 2. Reagents and conditions: (i) 4-Bromo-1-butene, Mg, Et₂O, 0 °C, 2 h, 50%; (ii) NaH, THF, 0 °C, HMPA, BnBr, 4 h, 95%; (iii) OsO₄, THF–H₂O (3:2), NaIO₄, 0 °C, 12 h, 80%; (iv) (a) ⁿBuLi, allyltriphenylphosphonium bromide, THF, 0 °C, 1 h, 62%; (b) ⁿBuLi, (2-methyl-2-propenyl)triphenylphosphonium bromide, THF, 0 °C, 1 h, 60%; (v) (a) 70% aq AcOH, rt, 12 h, 80% (R = H) and 70% (R = Me); (b) NaIO₄, THF–H₂O (3:2), 0 °C, 2 h, 75% (R = H) and 70% (R = Me); (vi) CH₂=CHMgBr, THF, –78 °C to rt, 55% (R = H) and 60% (R = Me); (vii) DMP, CH₂Cl₂, 0 °C to rt, 9 h, 85% (R = H) and 80% (R = Me).

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