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Catalytic enantioselective total synthesis of (+)-dumetorine by ring-rearrangement metathesis

Anke Rückert, Prashant H. Deshmukh and Siegfried Blechert*

Technische Universität Berlin, Institut für Chemie, Strasse des 17, Juni 135, D-10623 Berlin, Germany

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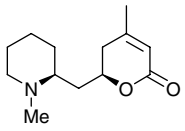
Abstract—A concise, enantioselective synthesis of (+)-dumetorine is described, giving the natural product in six steps and a 27% overall yield from a readily available precursor. Among the key steps used, the synthesis entails a high-yielding ring-rearrangement metathesis (RRM), using the commercially available first generation Grubbs catalyst **2** in combination with $Ti(O\textit{i}\text{–}Pr)_4$ as a co-catalyst. This constitutes the first enantioselective total synthesis of the alkaloid from a known chiral intermediate, and hence a confirmation of its absolute stereochemistry.

In recent years, ring-rearrangement metathesis (RRM) has developed into an effective synthetic strategy in alkaloid synthesis.[1–16] Typically, this transformation is used on strained cycloalkenes, which open and undergo metathesis to give either new rings and/or new side-chains. The net result is a defined but complex rearrangement of the carbon skeleton in one synthetic step. This approach is particularly suited to the incorporation of stereocentres, which can be set prior to RRM. Such transformations have typically been harnessed in the stereoselective synthesis of heterocycles. In our group, the enantioselective synthesis of a number of natural products has been elucidated. Recent examples include (+)-*trans*-195A,[2] (−)-lasubin II,[3] (−)-indolizidine 167B,[4] (+)-dihydrocuscohygrine,[5] cuscohygrine[5] and (−)-anaferine dihydrochloride.[6] Additional reports of RRM have been published from the groups of Plumet,[7] Grubbs,[8] Hoveyda,[9] Wright,[10] Hagiwara,[11] Lesma,[12] Koreeda,[13] Mariano[14] and Phillips.[15] More recently, we have also reported a diastereoselective RRM reaction.[16]

(+)-Dumetorine (**1**) was isolated in 1985 from the tubers of Dioscorea dumetorum Pax, a yam whose extracts have found an extensive use in African folk medicine and arrow poisons.[17] The only known previous synthesis of (±)-dumetorine used nitrone–olefin cycloaddition as the key step, confirming its structure and relative stereochemistry.[18] We now report the first enantioselective synthesis of the naturally occurring alkaloid using RRM as the key step, and thus provide a confirmation of its absolute stereochemistry.



(+)-dumetorine **1**

Numerous ruthenium catalysts have been developed in the last decade since the discovery of the 'first-generation' catalyst **2** by Grubbs and co-workers (Fig. 1).[19,20] These developments have largely been driven by the need for a higher activity, selectivity and greater functional group tolerance. However, no catalyst has yet proved to be universally superior. Given that most known ruthenium catalysts are derived from **2**, we wished to probe its effectiveness as a cheap, commercially available catalyst for RRM in the synthesis of **1**.

Retrosynthetically, the general connectivity of the target structure **1** is appropriate for an RRM strategy; however, the position of the double bonds and the choice of possible precursors require some consideration. We envisaged four plausible precursors for RRM (**8**–**11**, Scheme 1), which involve a disconnection on the piperidine ring either at C3–C4 or C4–C5, and

* Corresponding author. Tel.: +49 030 314 22355; e-mail: blechert@chem.tu-berlin.de

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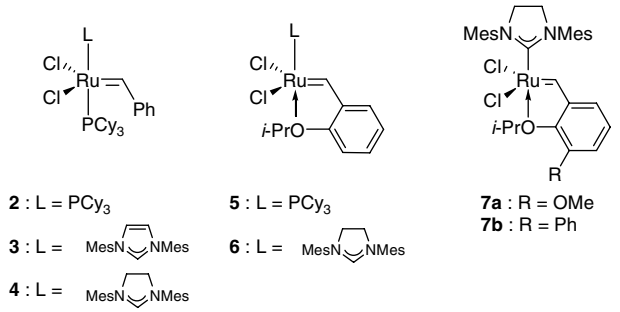
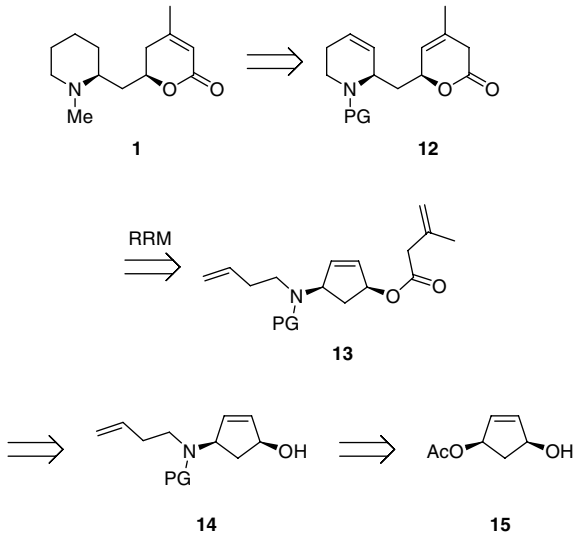


Figure 1. Ruthenium metathesis catalysts. Grubbs I (**2**),[19] Grubbs II (**3** and **4**),[21,22] Hoveyda I (**5**),[23] Hoveyda–Blechert (**6**),[23] *o*-methoxy-Hoveyda–Blechert (**7a**),[24a] *o*-phenyl-Hoveyda–Blechert (**7b**).[24b] Mes = mesityl(2,4,6-trimethylphenyl). Cy = cyclohexyl.

disconnections on the dihydropyranone either at C5′–C6′ or C4′–C5′; the latter disconnection would then require a migration of the double bond into conjugation with the ester group. The success of RRM reactions is often driven by the release of strain in the precursor. Therefore, based upon the ring strain inherent in cyclopentenes, and upon the perceived ease of an enantioselective synthesis, **11** was chosen as the most promising candidate for RRM in the synthesis of (+)-dumetorine (**1**).

The full retrosynthetic analysis is given in Scheme 2. Thus, the bicyclic ring system in **12** was to be obtained by RRM of the chiral, disubstituted cyclopentene **13**. This precursor was itself to be synthesized by sequential stereospecific amination[25] and esterification of the known cyclopentene **15**, which is readily accessible from enzymatic hydrolysis of its *meso* diacetate.[26] The removal of the protecting group on **12**, followed by N-methylation, selective double-bond migration to give the α,β-unsaturated lactone and selective reduction of the tetrahydropyridine ring was then to provide (+)-dumetorine **1** in a concise synthesis.

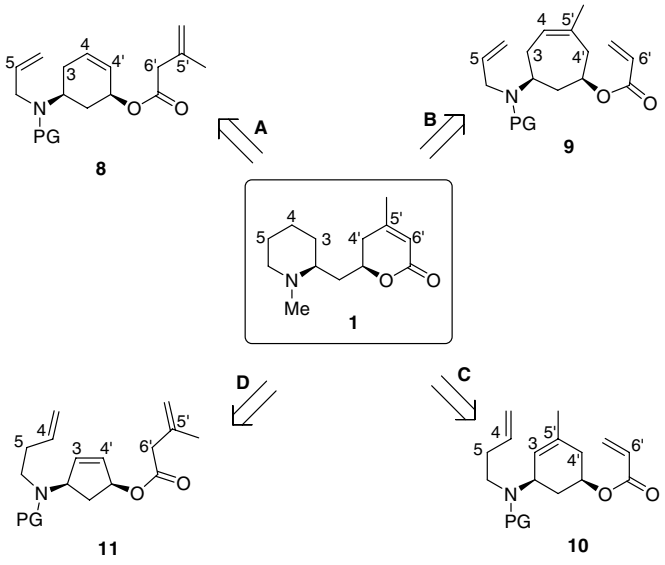
According to the synthetic plan outlined above, our synthesis commenced with the stereospecific palladium-



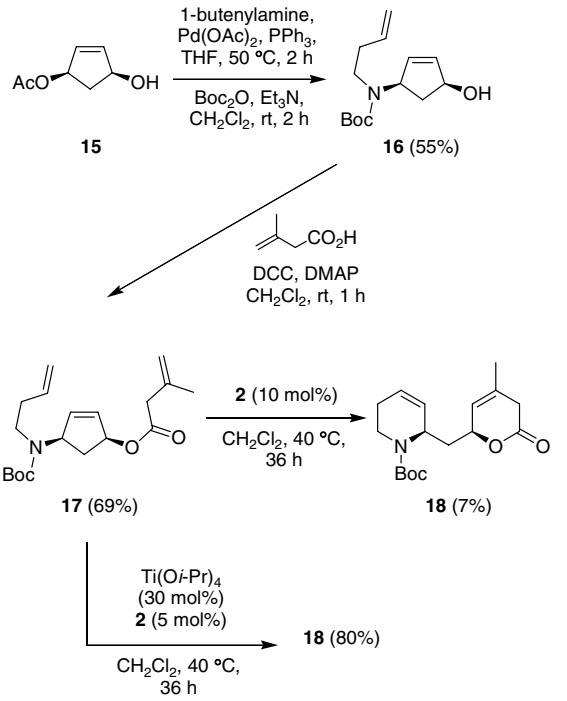
Scheme 2. Retrosynthetic analysis of (+)-dumetorine (**1**).

catalysed amination of the known allylic acetate **5**[26] (ee >99%) (Scheme 3). The treatment of **15** with 1-butenylamine, 25 mol % triphenylphosphine and 5 mol % palladium diacetate in THF gave the desired enantiomerically pure (ee >99%) amide **16** in a 55% yield, following N-protection with a *tert*-butyloxycarbonyl group.[25] The esterification of the allylic alcohol **16** with 3-methylbut-3-enoic acid using dicyclohexylcarbodiimide then gave the triene **17** in a 69% yield.

The preliminary investigation of the projected RRM reaction using 10 mol % of **2**[19] in refluxing CH_2Cl_2 gave only 7% of the desired heterocycle **18** after 36 h, while the starting material **17** was mostly recovered. This is in agreement with the observation made by Fürstner and Langemann, who report that certain ring-closing–ring-opening metathesis (RCM–ROM) reactions are disfavoured when the side-chain bearing the terminal double-bond is bound to the cyclic olefin by an ester

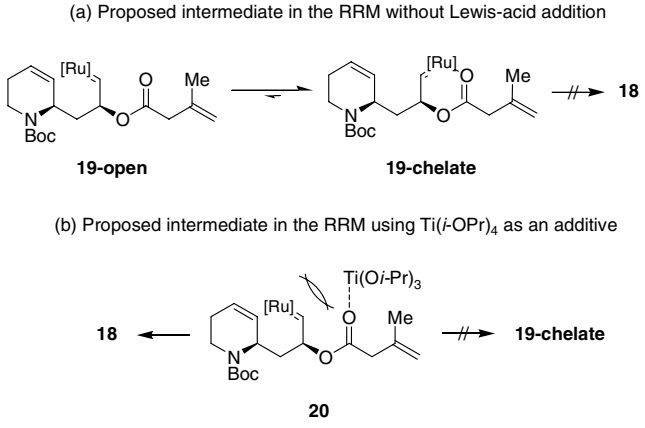


Scheme 1. Possible RRM strategies for the synthesis of **1**.



Scheme 3. Synthesis of RRM product **18**.

linkage.[27] Based upon this result, we attributed the low yield to the preferential formation of a stable cyclic carbene intermediate **19-chelate** (Scheme 4a), where the intermediate ruthenium carbene is chelated by the tethered ester moiety, thus inhibiting catalysis. However, titanium isopropoxide has been reported as an effective co-additive which suppresses the formation of such cyclic chelated intermediates, by competitively binding to such an ester functionality.[27] We reasoned that in this particular case, steric repulsion between the titanium and ruthenium moieties in **20** (Scheme 4b) may even favour the subsequent RRM steps by directing the carbene towards the adjacent endocyclic double bond. Indeed, we were pleased to find that using 30 mol % of titanium isopropoxide as a co-additive gave the desired ring-rearranged product **18** in a 80% yield, requiring the use of only 5 mol % of catalyst **2**.[28]

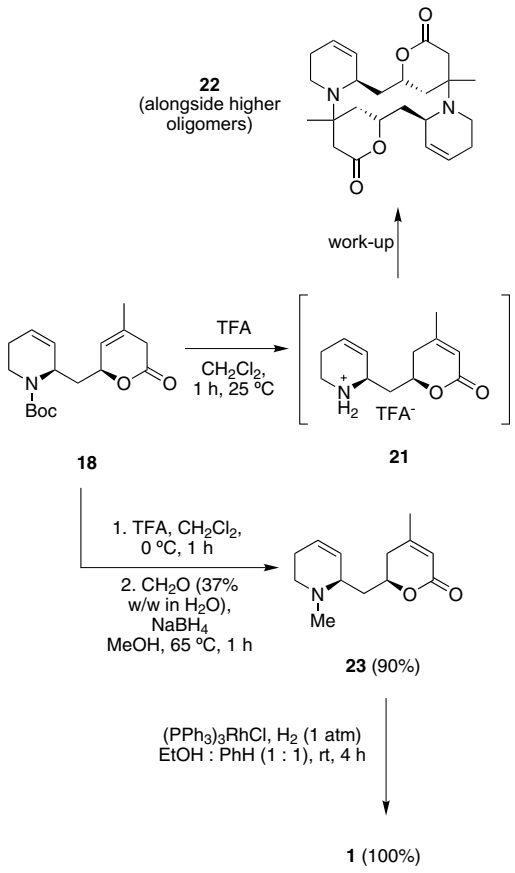


Scheme 4. Rationale for the enhanced RRM yield of **18** in the presence of Ti(O*i*–Pr)$_4$ as an additive.

With the ring-rearranged product **18** in hand, we turned our attention to the final steps in the synthesis of **1**. To our surprise, the desired product from the attempted *N*-Boc deprotection of **18** with TFA, decomposed rapidly to dimer **22** and to higher oligomers, upon attempted isolation of the free amine from its TFA salt. It is plausible that the double-bond isomerisation of the γ,δ-dihydropyranone had occurred during the deprotection under acidic conditions to give the conjugated dihydropyranone **21**. This may then have undergone self-Michael addition upon attempted neutralisation to its free amine. We bypassed this side reaction by performing the subsequent N-methylation in situ on the crude TFA salt. Thus, following acidic Boc-group cleavage, the solvents were evaporated and the crude salt was treated directly with aqueous formaldehyde in MeOH under Eschweiler–Clarke conditions, followed by a reduction of the intermediate amino alcohol with sodium borohydride. Gratifyingly, the desired N-methylated product **23** was isolated in a 90% yield from **18**. In early studies on an *N*-*o*-nitrophenylsulfinyl protected version of **18**, we found that the isomerisation of the double bond was sensitive to the conditions used. Using *p*-toluenesulfonic acid or rhodium trichloride, only a complex mixture of double-bond isomers were obtained. Under basic conditions using potassium *tert*-butoxide, the ring-opening of the dihydropyranone occurred. Ultimately, double bond isomerisation only occurred with the desired selectivity using the milder base DBU. Given the sensitivity of this system to double bond isomerisation conditions, we were pleased to note that our resultant synthetic route entailed the three synthetic transformations (Boc-deprotection, double-bond isomerisation and N-methylation) effectively in a high-yielding one-pot procedure.

We predicted that it would be possible to selectively reduce the double-bond in the tetrahydropyridine ring system of **23** in the presence of the double-bond in the dihydropyranone ring, since it is less sterically hindered and also nonconjugated. However, this was unsuccessful using various heterogeneous catalyst systems (Pd/$BaSO_4$; PtO_2; Pd/C), involving either hydrogen gas or secondary alcohols as the hydrogen source. In all cases, a nonselective reaction was observed and both double-bonds were reduced. We reasoned that since the dihydropyranone double-bond in **23** was sterically hindered by the methyl group, the use of a catalyst with a larger ligand sphere would result in chemoselectivity between the two double-bonds. Indeed, hydrogenation of **23** with the sterically encumbered Wilkinson's catalyst,[29] using hydrogen gas at 1 atm allowed the complete control of the chemoselectivity in the reduction and the desired natural product **1** was isolated quantitatively. All spectroscopic data were consistent with natural (+)-dumetorine {$[\alpha]_D$ +38 (*c* 2.1, $CHCl_3$), lit. $[\alpha]_D$ +40 (*c* 2.1, $CHCl_3$)}.[18] Since our enantioselective synthesis of **1** used the reported aminocyclopentene **16** as a chirally defined intermediate, we can now confirm the absolute stereochemistry of the natural (+)-dumetorine (**1**) as depicted (Scheme 5).

In summary, we have achieved the first enantioselective synthesis of (+)-dumetorine in seven linear steps with an



Scheme 5. Final steps in the synthesis of **1**.

overall yield of 27%. The key steps in this synthetic route have demonstrated the utility of ring-rearrangement metathesis for assembly of the two ring systems, using the relatively cheap, commercially available catalyst **2** aided by the presence of titanium isopropoxide, and the chemoselective, quantitative reduction between two endocyclic double-bonds to give (+)-dumetorine **1**, whose absolute stereochemistry has now been confirmed by total synthesis.

Acknowledgements

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet 2006.08.114.

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28. The procedure for RRM from **17** to **18**: In a glove-box, titanium isopropoxide (171 mg, 0.6 mmol) was added to ester **17** (675 mg, 2.0 mmol) in CH_2Cl_2 (180 mL), and the mixture stirred at 40 °C for 1 h. Grubbs catalyst **2** (83 mg, 0.1 mmol) was added and the mixture stirred at 40 °C for 36 h. The mixture was diluted in MTBE, filtered through silica gel, evaporated and chromatographed (hexanes/MTBE, 1:1) to give bicycle **18** (490 mg, 80%) as a clear, colourless oil: IR (thin film) 1740, 1690, 1652 cm^{-1}; $[\alpha]_D$ −110.5 (*c*, 2.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 5.83 (br s, 2H), 5.63 (br s, 2H), 4.96 (br s, 1H), 4.60 (br s, 1H), 2.98 (br s, 3H), 2.80 (m, 1H), 2.36 (s, 3H), 2.00 (m, 3H), 1.45 (s, 9H); ^{13}C NMR (67.5 Hz, $CDCl_3$) δ 169.3 (C_q), 120.3 (CH), 79.8 (CH), 76.5 (CH), 53.4 (CH_2), 40.0 (CH_2), 34.6 (CH_2), 28.4 (CH_3), 24.8 (CH_2), 21.5 (CH_3); HRMS (CI, NH_3) *m*/*z* calcd for $C_{19}H_{29}NO_4$ 335.2096, found: 335.2096.
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