Approach to the Core Structure of the Polycyclic Alkaloid Palhinine A

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Abstract: A synthesis of the tricyclic partly substituted core structure of palhinine A was achieved. To reach the bicyclo[2.2.2]octane motif a domino Michael reaction was employed as a key step. After Arndt–Eistert homologation and intramolecular aldol reaction the isotwistane core could be obtained after simple functional-group manipulations.

Key words: palhinine A, domino Michael reaction, X-ray crystal structure, Arndt–Eistert homologation, intramolecular aldol reaction

The $C_{16}N$-type alkaloid palhinine A (**1**, Figure 1) was described in 2010 as an isolate from the whole plant of *Palhinhaea cernua* L.[1] No significant biological activity was reported for this natural product, but the core or substructures thereof might serve as a scaffold for medicinal chemistry. The two contiguous quaternary stereocenters together with the polycyclic structure pose a great challenge for synthetic chemists. Recently, two synthetic studies were published by Chinese groups.[2,3] Thus, Xie and She et al. utilized an intramolecular Diels–Alder reaction of an *ortho*-quinone acetal to form the bicyclo[2.2.2]-octane core for the synthesis of tricyclic diketone **2**. In this case the five-membered ring originated from an intramolecular radical addition to a double bond.[2] In another study Fan et al. employed an intramolecular Diels–Alder reaction as well.[3] Here the five-membered ring of the isotwistane system was formed in the course of the cycloaddition reaction, eventually leading to core structure **3**. As a model study we targeted the partly substituted isotwistane core structure **5** of palhinine A. This was achieved via a domino Michael strategy followed by an Arndt–Eistert homologation and an intramolecular aldol reaction. Some selected examples of isotwistane formation are listed in the references.[3]

Our retrosynthetic analysis (Scheme 1) features an intramolecular aldol reaction to close the third ring to reach the tricyclic structure **6**. The required bicyclo[2.2.2]octane motif **7** could be established via a domino Michael reaction, a transformation which was broadly described in the literature,[4–6] followed by an Arndt–Eistert homologation.[7,8] As a starting material for the desired domino Michael reaction we needed cyclohexenone **8**, which would be obtained via addition of the Normant–Grignard[9] to vinylogous ester[10] **9**.

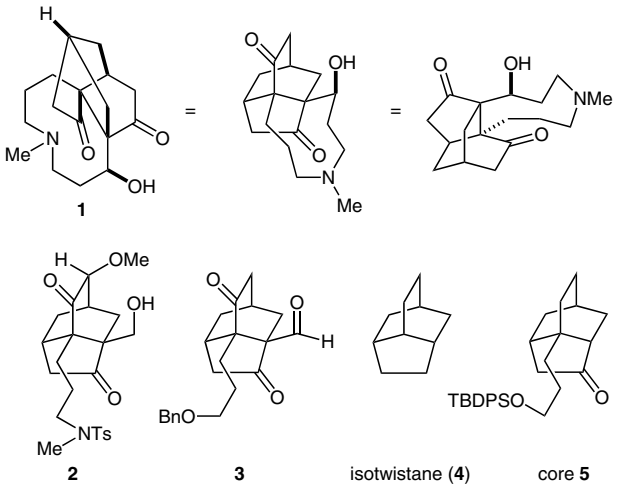
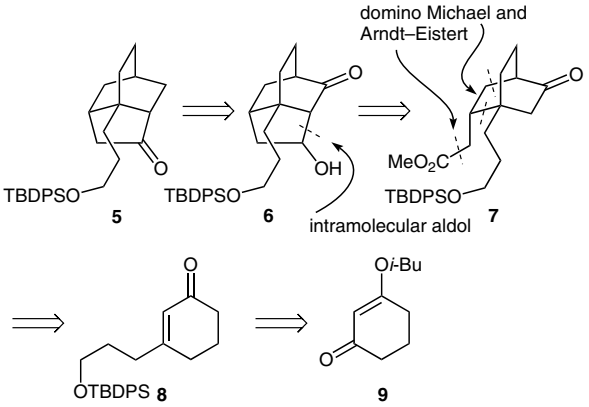


Figure 1 The structure of palhinine A (**1**) in three different views, already synthesized core structures **2** and **3**, isotwistane (**4**), and the target structure **5** of this work



Scheme 1 Retrosynthetic analysis for the palhinine A core **5**

The synthesis commenced with the addition of the Normant–Grignard,[9] which refers to the Grignard reagent prepared from 3-chloropropanol, to vinylogous ester **9** according to the literature (Scheme 2).[11,12] First, 1,2-addition to the carbonyl group occurred, followed by acidic hydrolysis of the vinylogous hemiacetal to form the desired hydroxyenone **10a**. We observed that a solution of **10a** in $CDCl_3$ partly converts into the spiroketone **10b**, probably via an acid-catalyzed intramolecular oxo-Michael addition.[11a] This intramolecular reaction also takes place in the purified product, so we always got a mixture of hydroxyenone **10a** and spiroketone **10b** for the subsequent step. This turned out to be inconsequential, because it was possible to use the mixture for the protection

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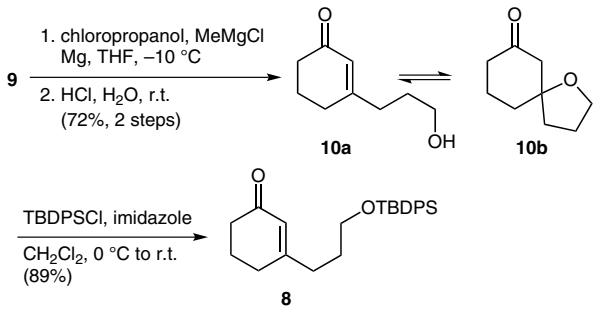
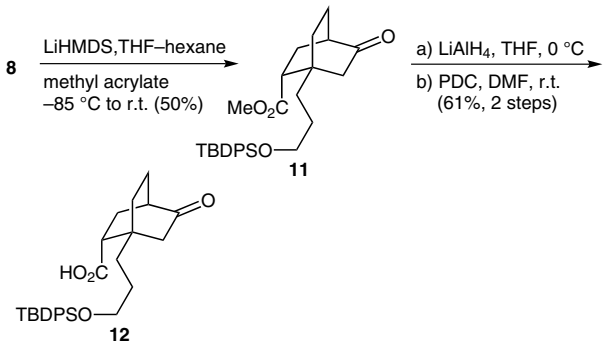
step with *tert*-butyldiphenylsilylchloride (TBDPSCl) giving good yields of silyloxyenone **8**. Thus, this intramolecular oxo-Michael reaction is reversible under the conditions of the protection reaction.



Scheme 2 Grignard addition to vinylogous ester **9** and conversion of the mixture of **10a**/**10b** into silyloxyenone **8**

The bimolecular domino Michael reaction[4] (Scheme 3) on cyclohexenone **8** was carried out under basic conditions with $LiN(SiMe_3)_2$ (LHMDS) as base and methyl acrylate (5 equiv). Use of LDA as base instead of LHMDS only led to poor yields. During the optimization of this reaction it turned out to be essential to use a mixture of THF and *n*-hexane as solvent. The reaction only led to one isomer **11** due to a chelating effect between the lithium ion and the carbonyl oxygen at the ring and the carbonyl oxygen of the ester group.[7] Standard ester cleaving conditions such as LiOH in THF–water or NaSEt in DMF or DMSO only led to decomposition or only to traces of product. The first successful attempt to cleave the ester in moderate yields was with Me_3SnOH.[13] But due to the high cost, high toxicity, high loading of the reagent (5 equiv), and the early stage in the synthesis we decided to look for another possibility to get the free acid. To save additional protection and deprotection steps we reduced the ketone and the ester function of bicyclic ester **11** to the corresponding diol using $LiAlH_4$ in one step, followed by a complete oxidation with PDC in DMF back to the keto acid **12** in 61% yield over two steps.

The stereochemistry of the bicyclic keto ester **11** could be proofed by a single-crystal X-ray analysis (Figure 2).



Scheme 3 Domino Michael reaction between enone **8** and methyl acrylate followed by ester cleavage via a reduction–oxidation sequence

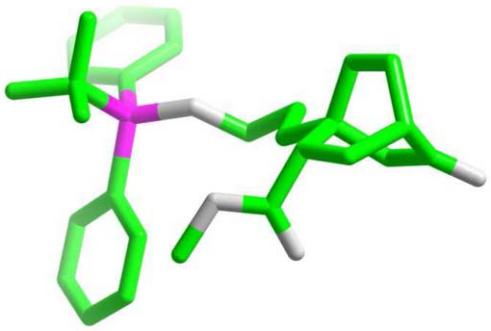
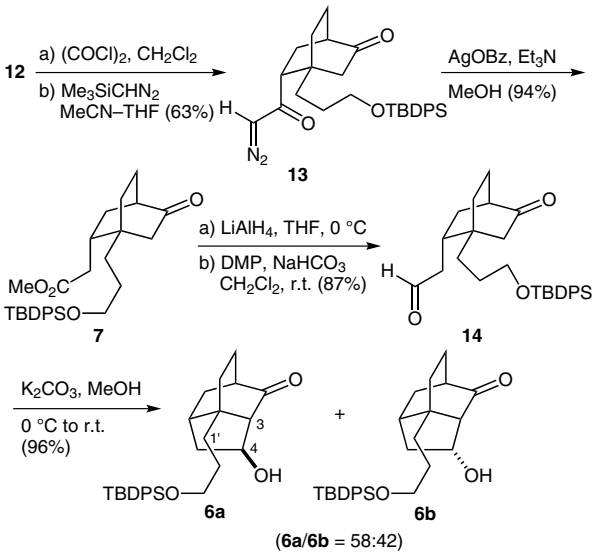


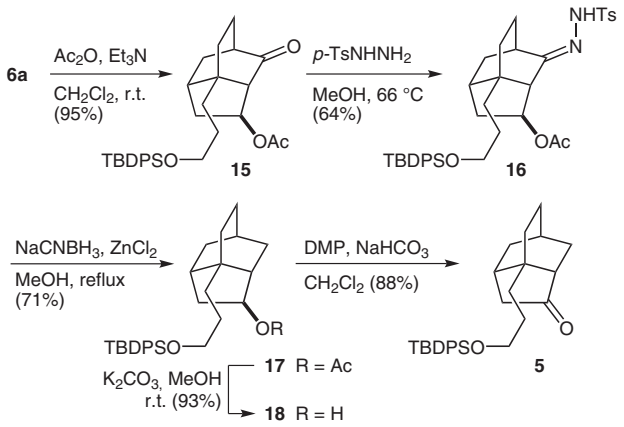
Figure 2 X-ray analysis of bicyclic ester **11**. The structure refinement was done using SHELXL-97.[14]

To perform the Arndt–Eistert homologation[4,5] (Scheme 4) we first prepared the acid chloride from **12** using oxalyl chloride and catalytic amounts of DMF. Reaction of the crude acid chloride with trimethylsilyldiazomethane produced the α-diazoketone **13**. Wolff rearrangement[8] of diazoketone **13** in methanol in the presence of silver benzoate under ultrasound irradiation provided an excellent yield of the homologated ester **7**. In order to convert keto ester **7** into keto aldehyde **14** we again relied on a redox sequence as before. Thus, full reduction of ester **7** to the corresponding diol with $LiAlH_4$ was followed by Dess–Martin oxidation[15] back to the keto aldehyde **14**. To close the third ring we performed an intramolecular aldol reaction with K_2CO_3 as base in methanol to furnish a mixture of the aldol products **6a**/**6b** with an *exo*/*endo* ratio of 1.35:1. Both epimers could be separated and characterized. In *endo*-aldol **6b** one proton on position 1′ showed a NOESY cross peak to the proton on position 4 and additionally the coupling constant between 3-H and 4-H was $^3J_{HH}$ = 7.6 Hz. In the *exo*-epimer **6a** there was no such NOESY cross peak, and the coupling constant between 3-H and 4-H was $^3J_{HH}$ = 0.9 Hz.



Scheme 4 Arndt–Eistert homologation of acid **12** to ester **7** and intramolecular aldol reaction of derived keto aldehyde **14** to tricyclic β-hydroxyketones **6a**/**6b**

Before forming a tosylhydrazone out of the ketone we needed to protect the alcohol function as acetate **15** (Scheme 5), because otherwise the conditions for tosylhydrazone formation led to decomposition. It was only possible to convert the *exo*-acetate **15** into the corresponding tosylhydrazone **16**. Subjecting the *endo*-acetate to the same reaction conditions led to decomposition, and only traces of the corresponding tosylhydrazone could be isolated. The next step was to reduce and defunctionalize the tosylhydrazone function in molecule **16** to a methylene group. This could be realized with the use of $NaCNBH_3$ and $ZnCl_2$ in methanol, and the acetate[16] **17** could be obtained in good yield.[17] Finally, after cleavage of the acetate of **17** with the use of K_2CO_3 in methanol, Dess–Martin oxidation[15] of alcohol **18** furnished the desired core structure **5** in good yield.[18]



Scheme 5 Conversion of the acetylated tricyclic aldol product **6a** into the palhinine A core **5**. DMP = Dess–Martin periodinane.

In conclusion, we achieved a racemic synthesis of the partly substituted isotwistane core structure **5** of palhinine A in 16 linear steps. Starting from vinylogous ester **9** we obtained the bicyclo[2.2.2]octane motif **11** by exploiting a domino Michael reaction. By means of single-crystal X-ray structural analysis the stereoselectivity of the domino Michael reaction could be proofed. The best yields in cleaving the ester **11** were achieved via reduction followed by oxidation. After Arndt–Eistert homologation, reduction, and oxidation to the aldehyde **14**, an intramolecular aldol reaction furnished the tricyclic isotwistane structures **6a**/**6b**. From there palhinine A core structure **5** could be obtained by deoxygenation and oxidation of the secondary alcohol in the five-membered ring.

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(16) **Acetate 17**
To a solution of tosylhydrazone **16** (182 mg, 270 μmol) in abs. MeOH (3 mL) were added anhyd $ZnCl_2$ (44 mg, 703 μmol, 2.6 equiv) and $NaCNBH_3$ (59 mg, 433 μmol, 1.6 equiv) at r.t. The reaction was then stirred at reflux temperature for 3.5 h. Then additional $NaCNBH_3$ (59 mg, 433 μmol, 1.6 equiv) was added and reflux was continued for 2 h. Thereafter, the mixture was cooled to r.t. and treated with aq NaOH (10 mL, 1 M) and sat. NaCl solution (10 mL). The milky mixture was extracted with EtOAc (3 × 40 mL). The combined organic layers were dried over Na_2SO_4, filtered, concentrated in vacuo, and purified by flash chromatography (1.5 × 15 cm, PE–EtOAc, 10:1 to 0:1) to give 94 mg (192 μmol, 71%) of acetate **17** as a colorless oil; R_f = 0.63 (cyclohexane–EtOAc = 2:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.05 (s, 9 H, $H_{t\text{-Bu}}$), 1.16–1.31 (m, 2 H, 2′-H, 10-H), 1.35–1.64 (m, 9 H, 1-H, 1′-H, 2′-H, 5-H, 8-H, 9-H), 1.73–1.95 (m, 9 H, 2-H, 3-H, 5-H, 6-H, 10-H, CH_3CO_2), 3.56–3.69 (m, 2 H, 3′-H), 4.89–4.96 (m, 1 H, 4-H), 7.34–7.45 (m, 6 H, H_{Ar}), 7.65–7.70 (m, 4 H, H_{Ar}). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.2 [$C(CH_3)_3$], 21.3 (CH_3CO_2), 24.0 (C-8), 24.0 (C-1), 26.9 [$C(CH_3)_3$], 27.3 (C-1′),28.6 (C-9), 33.2 (C-2′), 34.4 (C-5), 37.1 (C-10), 38.5 (C-6), 40.7 (C-7), 41.1 (C-2), 44.9 (C-3), 64.8 (C-3′), 85.3 (C-4), 127.6 (C_{Ar}), 129.5 (C_{Ar}), 134.1 (C_{Ar}), 134.1 (C_{Ar}), 135.5 (C_{Ar}), 170.9 (CH_3CO_2). HRMS: calcd for $C_{31}H_{42}O_3Si$ [M + Na]$^+$: 513.279543; found: 513.279442.
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(18) **Ketone 5**
To a solution of alcohol **18** (58 mg, 129 μmol) in abs. CH_2Cl_2 (1.3 mL) were added $NaHCO_3$ (43 mg, 517 μmol, 4 equiv) and DMP (71 mg, 168 μmol, 1.3 equiv) at r.t. After 1 h at r.t. DMP (71 mg, 168 μmol, 1.3 equiv) was added. After additional 30 min at r.t. sat. aq $NaHCO_3$ solution (2 mL) and sat. aq $Na_2S_2O_3$ solution (2 mL) were added, and the mixture was stirred for 30 min. H_2O (5 mL) was added, and the mixture was extracted with Et_2O (3 × 15 mL). The combined organic layers were washed with sat. NaCl solution (10 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (1.5 × 15 cm, PE–EtOAc = 8:1) to give 51 mg (114 μmol, 88%) of tricyclic ketone **5** as a colorless oil; R_f = 0.45 (cyclohexane–EtOAc, 5:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.04 (s, 9 H, $H_{t\text{-Bu}}$), 1.08–1.28 (m, 2 H, 1′-H), 1.36–1.72 (m, 9 H, 1-H, 2-H, 2′-H, 8-H, 9-H, 10-H), 1.79–2.05 (m, 4 H, 2-H, 3-H, 5-H, 10-H), 2.13–2.21 (m, 1 H, 6-H), 2.42 (dd, *J* = 7.2, 18.8 Hz, 1 H, 5-H), 3.53–3.66 (m, 2 H, 3′-H), 7.33–7.46 (m, 6 H, H_{Ar}), 7.60–7.68 (m, 4 H, H_{Ar}). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.1 [$C(CH_3)_3$], 24.0 (C-8), 24.3 (C-1), 26.8 [$C(CH_3)_3$], 27.1 (C-2′), 28.0 (C-9), 30.5 (C-2), 33.7 (C-1′), 35.0 (C-6), 36.5 (C-10), 38.6 (C-7), 45.4 (C-5), 51.5 (C-3), 64.1 (C-3′), 127.6 (C_{Ar}), 129.5 (C_{Ar}), 133.9 (C_{Ar}), 135.5 (C_{Ar}), 222.4 (C-4). HRMS: *m/z* calcd for $C_{29}H_{38}O_2Si$ [M + Na]$^+$: 469.253328; found: 469.253565.

