Total Synthesis of (±)-Ceratopicanol: Application of Pd-Catalyzed Enediyne Cycloreduction

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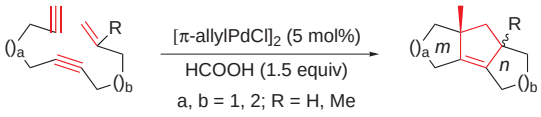
Abstract: Pd-catalyzed cycloreduction of enediyne **3** successfully afforded the linear triquinane skeleton **4**. Total synthesis of (±)-ceratopicanol was accomplished using additional eight-step transformations starting from **4**.

Key words: ceratopicanol, palladium, enediyne, cycloreduction, triquinane

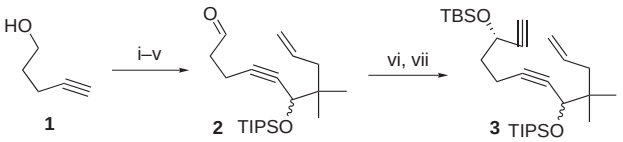
In 1996, we reported Pd-catalyzed cycloreduction of enediynes affording [m,5,n]-tricyclic compounds (Equation 1).[1] The reaction indeed proceeds with high levels of chemo- and stereoselectivities and is accompanied by a significant increase in structural complexity. We have utilized this method to synthesize members of the triquinane natural products and here wish to report a highly efficient synthesis of (±)-ceratopicanol.



Equation 1

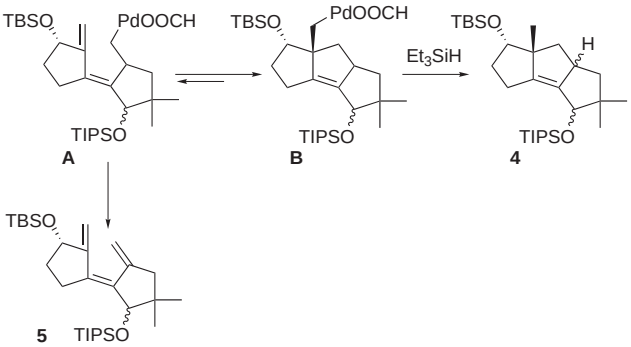
Ceratopicanol, isolated from the fungus *Ceratocystis piceae* Ha 4/82 by Hanssen and Abraham in 1988,[2] has an attractive synthetic challenge due to the uncommon presence of two vicinal bridgehead quaternary carbons among the five contiguous chiral centers, on a *cis*,*anti*,*cis*-triquinane framework.[3] Its structure represents evidence for the biosynthetic generation of hirsutene and related natural products associated with the humulene cascade.[4] By now, six groups reported total syntheses of ceratopicanol that span from a low of 7 to a high of 21 synthetic steps in varying efficiencies.[5] Our synthesis of (±)-ceratopicanol began with enediyne **3**, which was readily prepared from 4-pentyn-1-ol in very common processes (Scheme 1).

Transformation of 4-pentyn-1-ol (**1**) into the aldehyde **2** was conducted: THP-protection of the hydroxyl group, coupling of its terminal carbon with 2,2-dimethyl-4-pentenal, TIPS-protection of the newly formed hydroxyl group, deprotection of THP into the alcohol,[6] and PDC oxidation. The aldehyde **2** was coupled with ethynylmagnesium bromide and again protected its hydroxyl group with *tert*-butyldimethylsilyl chloride to give the enediyne **3** in multi-gram scale. The seven-step overall yield from **1** to **3** was 38%. In real syntheses, multi-gram scale preparation of **3** was accomplished with only one purification step for the aldehyde **2** during these processes.



Scheme 1 Preparation of enediyne **3**. *Reagents and conditions*: (*i*) DHP, TsOH (cat), CH_2Cl_2, r.t., 2 h (98%): (*ii*) *n*-BuLi, 2,2-dimethyl-4-pentenal, THF, –78 °C (80%); (*iii*) $(i\text{-Pr})_3SiOTf$, 2,6-lutidine, CH_2Cl_2, r.t., 2 h (92%); (*iv*) TsOH (cat.), *i*-PrOH, r.t., 4 h, (88%); (*v*) PDC, CH_2Cl_2, r.t., 10 h (86%); (*vi*) ethynylmagnesium bromide, THF, 0 °C, 2 h (78%); (*vii*) *t*-$BuMe_2SiCl$, imidazole, DMF, r.t., 6 h (90%).

The next challenge was to transform enediyne **3** into the tricycle **4**. Pd-catalyzed cycloreduction of **3** under our reported conditions gave a mixture of tricycle **4** in only 35% yield along with unidentified products.[1] This was fair enough but had to be improved its chemical yield. A major problem was found to arise from competitive β-elimination of the alkylpalladium intermediates ***A*** which could be prone to undergo β-elimination to form the triene **5** as shown in Scheme 2.[7]



Scheme 2 Pd-catalyzed cycloreduction of enediyne **3** to **4**.

We believe that the intermediate ***A*** undergoes two pathways: one to thermodynamically stable triene **5** and the other to kinetically facile cyclopentenylmethyl intermediate ***B***.[1] To facilitate formation of **4**, a stronger reductant was required to cleave the carbon–Pd bond of ***B***. Thus, we have attempted optimization studies by adding reductants

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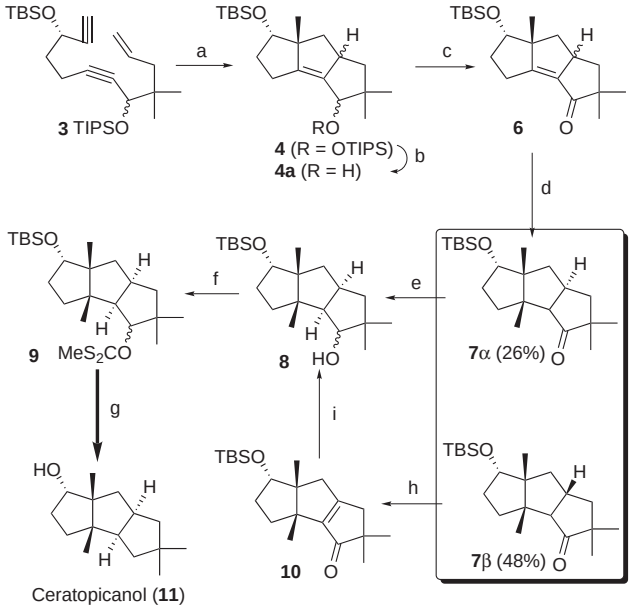
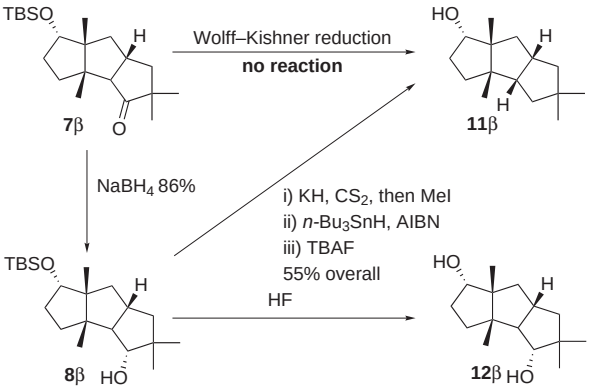
as well as by changing reaction temperature and solvents. After all, a catalytic mixture of $[(\pi\text{-allyl})PdCl]_2$ (5 mol%), PPh_3 (20 mol%), HCOOH (1.0 equiv), and triethylsilane (10 equiv) in 1,4-dioxane, was found to transform enediyne **3** to the cycloreduced tricycle **4** in 70–75% yield (α:β ratio of angular H = 1:3) along with only a little amount of **5**.[8] Although eight racemic products could be formed due to four stereogenic centers, only four tricyclic products were generated with *anti*-relationship between TBSO group and the angular methyl group. Gratifyingly, we were able to obtain **4** in multi-gram quantity from each trial, which was important in early stage in multi-step syntheses.

With the tricyclic compound **4** in hand by using our Pd-catalyzed cycloreduction methodology as a key step, we could attempt a total synthesis of (±)-ceratopicanol, a triquinane sesquiterpene as shown in Scheme 3.



Scheme 3 Total synthesis of (±)-ceratopicanol. *Reagents and conditions*: (*a*) 5 mol% $[(\pi\text{-allyl})PdCl]_2$, 20 mol% PPh_3, 1.0 equiv HCOOH, 10 equiv Et_3SiH, 1,4-dioxane, 80 °C, 20 h (70%); (*b*) TBAF, THF (83%); (*c*) $(COCl)_2$, DMSO, then Et_3N, CH_2Cl_2, –78 °C (88%); (*d*) $Me_2CuMgBr$, THF,–78 °C to r.t. (74%); (*e*) DIBAL, THF, 0 °C, 1 h (90%); (*f*) KH, CS_2, then MeI, THF (95 %); (*g*) *n*-Bu_3SnH, AIBN (cat.), toluene, reflux, 30 min, then TBAF, THF, reflux, 2 h (64%); (*h*) LDA, PhSeCl, –78 °C, then H_2O_2, CH_2Cl_2, r.t., 2 h (82%); (*i*) Li, NH_3, *t*-BuOH, –78 °C, 20 min (55 %).

Selective deprotection of TIPS group of **4** by using one equivalent TBAF in THF afforded **4a** which was then oxidized to give a 1:3 diastereomeric mixture of enone **6**. Introduction of a bridgehead quaternary methyl group was cleanly conducted by using classical magnesium dimethylcuprate in THF at –78 °C in 74% yield.[9] At this stage, we needed to separate two diastereomers, one of which had to be altered its ring configuration. Based on 2D NMR analysis of related compounds done by us in 1996, the major isomer was believed to have a *cis*,*trans*,*cis* ring configuration, which matched with that of ceratopicanol. However, the major isomer **7β** was proven to have a *cis*,*cis*,*cis* configuration by 2D-NOESY experiments, which was confirmed by X-ray crystal structure of its derivative **12β**. In the beginning of this synthesis, deoxygenation of **7β** was attempted, since we assumed that **7β** had the correct configuration with that of ceratopicanol (Scheme 4). Its Wolff–Kishner deoxygenation did not occur.[10] Its reduction with sodium borohydride furnished alcohol **8β** (86%) and the following Barton–McCombei deoxygenation and desilylation were carried out successfully to give **11β** in 55% yield. Since ^1H NMR data of **11β** were different from reported data of ceratopicanol, we elucidated a structure of **12β**, the desilylated compound of **8β**, by X-ray study as shown in Figure 1.



Scheme 4 Conversion of **7β** to **11β**.

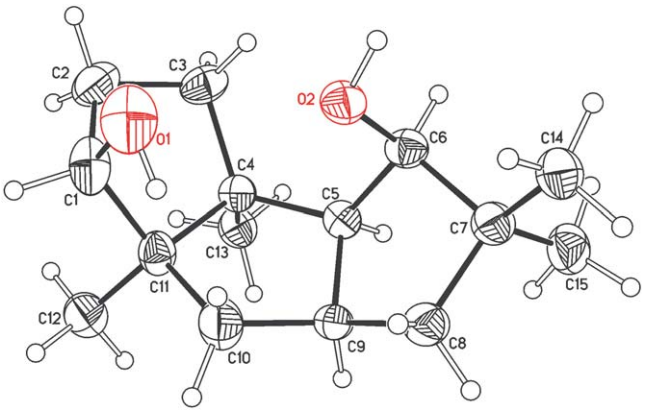


Figure 1 X-ray structure of **12β**.

A remaining problem was how to utilize **7β** in this synthesis. We could convert **7β** to the enone **10** by α-selenylation followed by oxidative elimination in one-pot process.[11] Lithium reduction of **10** in liquid ammonia gave the alcohol **8** as per Mehta's synthesis.[5f,12] Overall yield from **7β** to **8** was 45%.

Complete synthesis of ceratopicanol from **7α** was accomplished by deoxygenation using known methods.[13] Reduction of **7α** with DIBAL to the alcohol **8** (1:9) and its xanthate formation of **8** to **9** were easily conducted. Reduction using tributyltin hydride smoothly occurred in refluxing toluene in the presence of a catalytic amount of

AIBN. Chromatographic purification of TBS-protected ceratopicanol resulted in failure due to difficulty in removing tributyltin hydride and its derivatives.[14] Thus, upon completion of the reduction, the reaction mixture was concentrated under reduced pressure, dissolved in THF, and refluxed in the presence of TBAF. Due to high affinity between tin and fluoride, this process could afford pure (±)-ceratopicanol (**11**) as a colorless oil in 64% yield, whose ^{1}H NMR data were identical to reported data.[15] Finally, we decided this synthesis using the mixture of **7α** and **7β** without separation. About 1:3 mixture of **7α** and **7β** was converted to the enone **10** and dissolving metal reduction to alcohol **8**, and the following Barton–McCombie reduction and desilylation gave (±)-ceratopicanol in similar yield based on a mixture of **7α** and **7β**. Overall, this synthesis based on Pd-catalyzed cycloreduction as a key step is composed of eight highly efficient steps and furnished (±)-ceratopicanol in overall 13–15% yield based on the enediyne **3**.

In conclusion, we accomplished the total synthesis of ceratopicanol in eight steps with 14% overall yield based on readily prepared endiyne **3**. Most steps were composed of highly efficient procedures. Finally, we wish to note that Pd-catalyzed cycloreduction of enediyne **3**, leading to the key skeleton of the triquinane natural products, made this synthesis highly efficient and practical method over the reported syntheses to date.

Acknowledgment

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(15) All new compounds were fully characterized by ^{1}H NMR, ^{13}C NMR, IR, HRMS (or elemental analysis).
Ceratopicanol (11): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.71 (dd, *J* = 10.0, 7.2 Hz, 1 H), 2.49 (m, 1 H), 2.34 (ddd, *J* = 11.3, 8.3, 8.3 Hz, 1 H), 2.15 (dd, *J* = 14.0, 9.6 Hz, 1 H), 1.88 (m, 1 H), 1.67 (ddd, *J* = 13.0, 8.4, 1.2 Hz, 1 H), 1.56 (m, 1 H), 1.50–1.32 (m, 5 H), 1.23 (dd, *J* = 13.0, 4.8 Hz, 1 H), 1.08 (dd, *J* = 13.8, 6.8 Hz, 1 H), 1.04 (s, 6 H), 0.88 (s, 3 H), 0.87 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 82.62, 58.80, 54.96, 51.23, 48.77, 44.18, 41.94, 41.68, 40.85, 39.56, 31.54, 30.60, 28.54, 23.66, 21.25. FT-IR (neat): 3310 (–OH, br s) cm^{-1}.
Isomer of Ceratopicanol (11β): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.88 (m, 1 H), 2.64 (h, *J* = 8.0 Hz, 1 H), 2.45 (dt, *J* = 11.2, 9.6 Hz, 1 H), 2.08 (dtd, *J* = 13.6, 9.2, 5.6 Hz, 1 H), 1.79 (ddd, *J* = 11.6, 11.4, 5.6 Hz, 1 H), 1.65–1.54 (m, 2 H), 1.46 (s, 1 H), 1.44 (s, 1 H), 1.38 (ddd, *J* = 12.8, 8.8, 2.0 Hz, 1 H), 1.31 (d, *J* = 4.0 Hz, 1 H), 1.28 (m, 1 H), 1.11–1.06 (m, 2 H), 1.04 (s, 3 H), 0.95 (s, 3 H), 0.91 (s, 3 H), 0.79 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 81.16, 59.62, 54.63, 52.27, 49.83, 44.25, 41.44, 40.97, 39.85, 32.81, 30.25, 29.35, 28.15, 23.69, 19.63. FT-IR (neat): 3320 (–OH, br s) cm^{-1}. HRMS (ES): *m/z* calcd for $C_{15}H_{26}ONa^+$: 245.1881; found: 245.1872.