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Synthesis of natural products via stereocontrolled palladium-catalyzed reactions*

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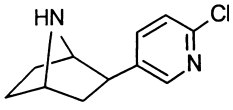
Abstract: Stereocontrolled palladium-catalyzed reactions were employed in the stereoselective synthesis of some natural products. Thus (±)-epibatidine (–) paeonilactone A (and B), and (–)-conduritol C, and (+)-monomorine I were synthesized.

General methodology for the synthesis of natural products with efficient control of 1,4 relative stereochemistry has been developed in our laboratory [1]. This approach is based on palladium-catalyzed 1,4-oxidation of 1,3-dienes with subsequent allylic fanctionalization and has proven to be powerful in stereoselective synthesis [2,3].

SYNTHESIS OF EBIBATIDINE AND ANALOGUES

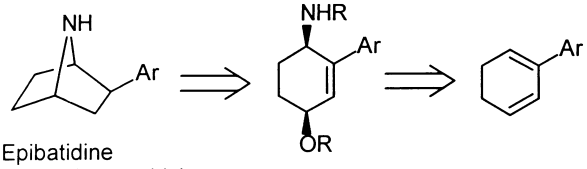
Epibatidine was isolated in 1992 from the skin of the Ecuadorian poison frog *Epipedobates tricolor* by Daly and co-workers (Scheme 1) [4]. It was found to be a highly potent analgesic and in tests of analgesic properties it was >200 times as active as morphine. It is a nonopioid analgesic and acts as a nicotine acetylcholine receptor antagonist. Since its isolation and characterization there has been a great interest in the synthesis of epibatidine. Up to date around 30 papers have dealt with the synthesis of Epibatidine and analogues [5]. A review from 1994 covers the first nine syntheses [5a].



Epibatidine

Scheme 1

The synthesis of epibatidine and analogues described below [6] is based on the palladium-catalyzed 1,4-functionalization of 1,3-dienes and a retrosynthetic analysis is shown in Scheme 2. The bicyclic system could be obtained from cyclization of a 1,4-aminoalcohol derivative, which in turn is accessible from the 2-aryl-1,3-diene via the 1,4-functionalization methodology [3]. Our methodology allows a full control of the stereochemistry ofthe aminoalcohol derivative, e.g. the amino and oxygen groups can be introduced in either a *cis* or *trans* fashion.

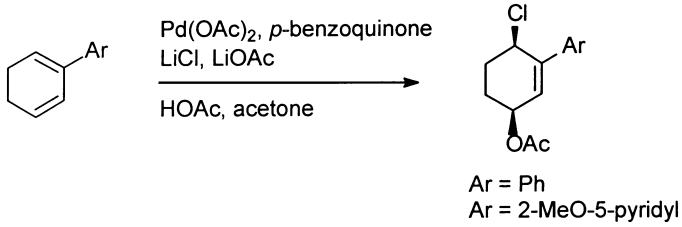


Epibatidine
Ar = 2-Cl-5-pyridyl

Scheme 2

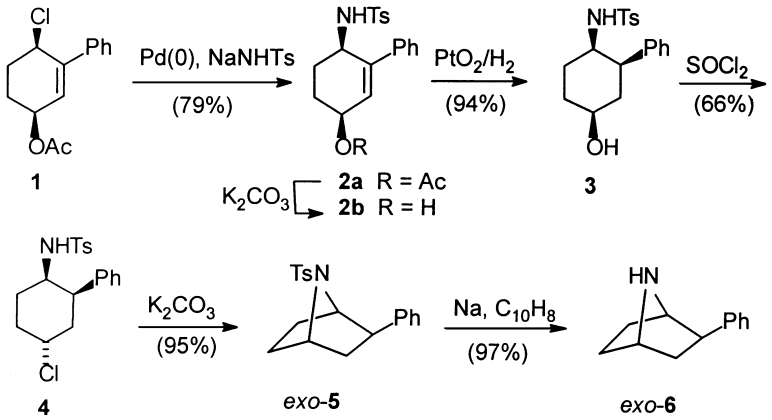
* Invited Lecture presented at the 21st IUPAC International Symposium on The Chemistry of Natural Products (ISCNP-21), Beijing, China, 11–16 October 1998, pp. 1025–1166.

A general method for the synthesis of 2-aryl-1,3-dienes based on a copper-catalyzed coupling of the dienyl triflates from 2-cyclohexenone was recently developed in our laboratory [7]. The requisite aryldienes were prepared according to that method or via Grignard addition to 2-cyclohexenone and subsequent elimination. Palladium-catalyzed chloroacetoxylation of 2-phenyl-1,3-cyclohexadiene afforded the chloro acetate in a highly stereo- and regioselective reaction in 62% yield (Scheme 3). The corresponding chloroacetoxylation of the pyridyl derivative was also regio-and stereoselective but the yield was moderate (30%)



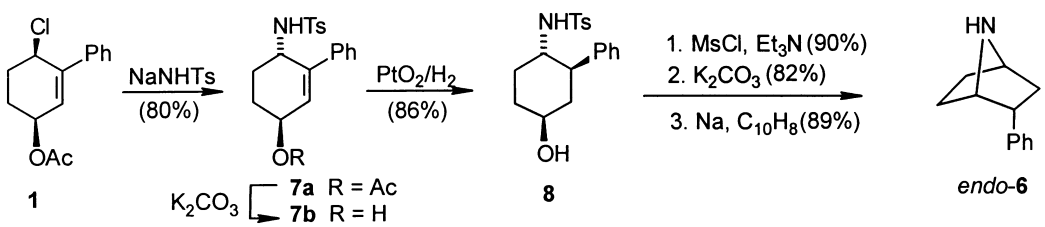
Scheme 3

Further functionalization of the 2-phenyl-1,4-chloroacetate **1** is shown in Scheme 4. Palladium-catalyzed nueleophilic substitution of the allylic chloride proceeded with retention of configuration at carbon to produce the aminoalcohol derivative **2**. Subsequent hydrogenation of the double bond was highly selective and took place from the less sterically hindered face of the molecule to give the overall *cis* compound **3** in excellent stereoselectivity and yield. In this way the *cis* stereochemistry between the phenyl and tosylamido groups required for the exo compound was created. For the cyclization it was necessary to invert at the oxygen center, which was done by $SOC1_2$ to give **4**.



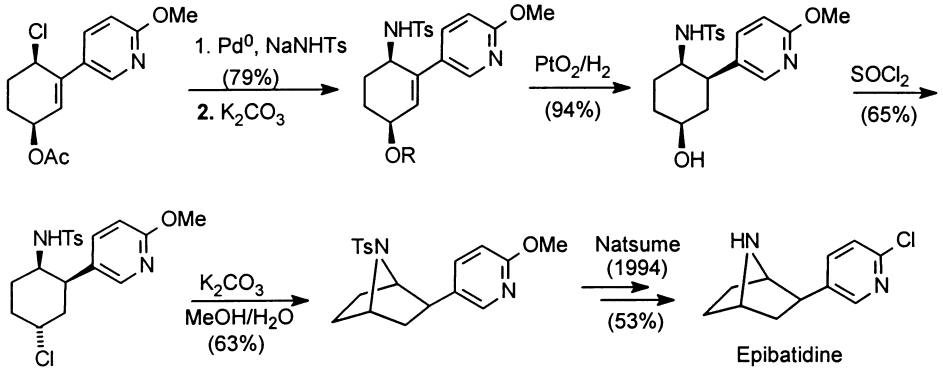
Scheme 4

The corresponding endo isomer *endo*-**6** was synthesized according to Scheme 5. In this case the *trans*-aminoalcohol derivative was prepared by employing a classical S_N2 reaction in the substitution of the chloride by tosyl amide. For the endo isomer a *trans* relationship between the nitrogen and the phenyl group is required. Interestingly, we found that hydrogenation of **7b** employing Adam's catalyst was highly stereoselective and occurred syn to the tosylamido group to produce the desired *trans* relationship between nitrogen and phenyl. Subsequent mesylation of **8** and cyclization afforded the tosyl protected bicyclic compound, which was deprotected to give the endo isomer *endo*-**6**.



Scheme 5

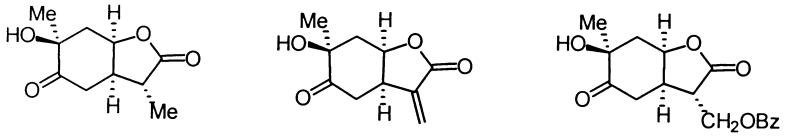
Finally, epibatidine was synthesized. (Scheme 6) [6]. The same strategy as for the synthesis of the exo phenyl derivative *exo*-**6** was employed. Also in this case the hydrogenation was highly stereoselective.



Scheme 6

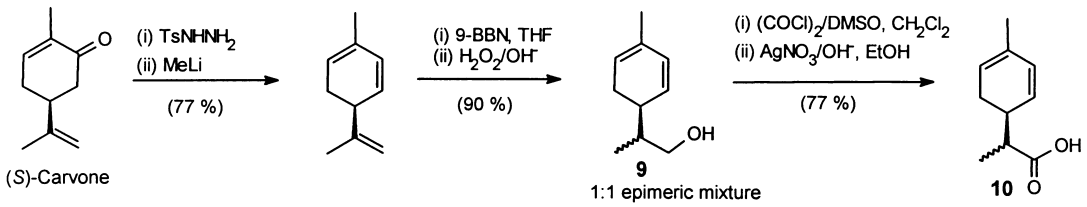
SYNTHESIS OF PACONILACTONES

In traditional Japanese and Chinese medicine Paeony root (*Paeoniae Radix*) is used for treatment of pain in the abdominal region. From extracts of this root Paeonilactones A, B and C have been isolated (Scheme 7) [8]. Interestingly, extracts have been shown to improve the cognitive disruption caused by central cholinergic dysfunction, which is indicating its potential for therapy of Alzheimer's disease [8b]. The Paeonilactone structure element would be readily obtained from palladium-catalyzed oxylactonization of enantiomericaly pure diene acid **10**, which is readily accessible from commercially available (*S*)-Carvone according to Scheme 8. A Shapiro reaction followed by hydroboration/oxidation afforded the diene alcohol **9** Mild oxidation of the alcohol afforded the enatiomerically pure acid **10** in 77% yield as a 1:1 epimeric mixture.



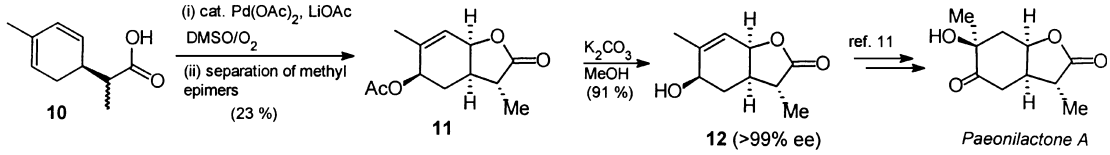
Paeonilactone A *Paeonilactone B* *Paeonilactone C*

Scheme 7



Scheme 8

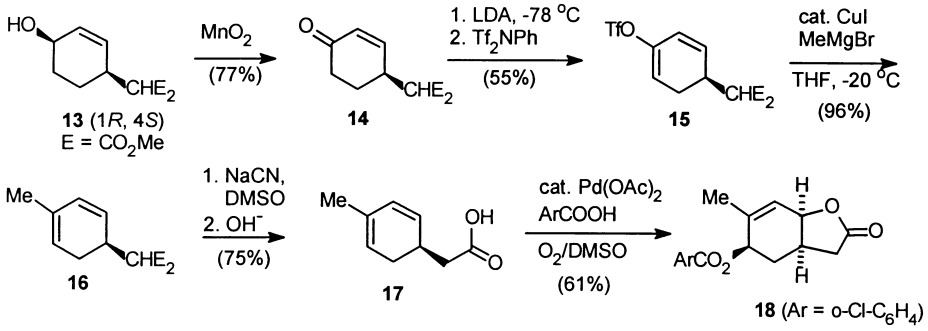
Cyclization of the diene acid **10** was pursued according to a recently developed modification [9] of the palladium-catalyzed 1,4-oxylactonization reaction in which $Pd(OAc)_2$ and molecular oxygen in DMSO are employed. This reaction is thought to involve colloidal palladium. Under these reaction conditions highly selective 1,4-*cis* addition occurs. The overall yield is about 50%, but because of the 1:1 epimeric mixture of the starting diene acid only 23% of the desired epimer **11** was obtained. Hydrolysis gave the known lactone alcohol **12**, which was shown to be of >99% enantiomer excess [10]. This alcohol has previously been transformed to Paeonilactone A and B by Kadota *et al.* [11] (Scheme 9).



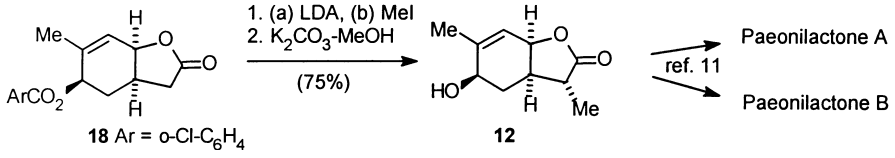
Scheme 9

Because of the problems with epimers an alternative approach was also developed (Scheme 10) [12].

Enantiomerically pure malonate alcohol **13** (>98% enantiomer excess) is readily available from 1,3-cyclohexadiene via palladium-catalyzed 1,4-functionalization in combination with enzymatic hydrolysis [13]. Oxidation to the ketone (**14**) and formation of the kinetic enol triflate **15** provided a useful starting material for a copper catalyzed cross coupling. Reaction of diene trifiate **15** with methyl magnesium bromide in the presence of catalytic amounts of copper iodide afforded the methyl diene **16** in excellent yield. Subsequent decarboxylation and Pd-catalyzed lactonization of **17** employing the aerobic method in DMSO afforded the lactone **18** in 61% yield (Scheme 10). The lactone 18 was transformed to Paeonilactone A and B according to Scheme 11. The methyl group was stereoselectively introduced by reaction of the lactone enolate with methyl iodide. The lactone alcohol **12** has previously been transformed to Paeonilactone A and B by Kadota *et al*. [11].



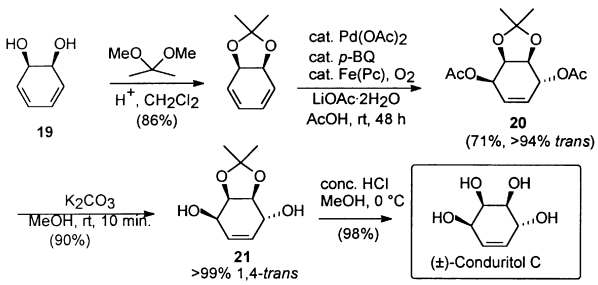
Scheme 10



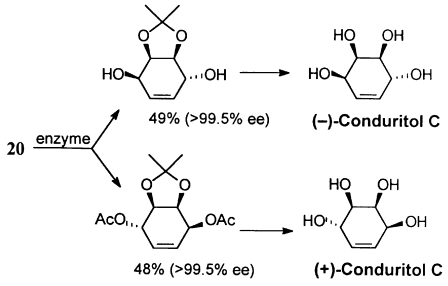
Scheme 11

SYNTHESIS OF CONDURITOL C

Conduritols constitute a class of cyclohexenetetroles with interesting biological activity including antibiotic, anti-leukemic, and tumor inhibitory activity. There are six possible diastereoisomers of conduritol and they are named conduritol A, B. C, D, E and F. The syntheses of (±)-conduritol and enantiomerically pure (+)- and (–)-conduritol are shown in Schemes 12 and 13, respectively. Commercially available cyclohexadienediol **19** was protected as acetonide followed by palladium-catalyzed aerobic 1,4-diacetoxylation to give *trans*-diacetate **20** in 71% yield (>94% *trans*). Hydrolysis and purification of the diol gave 90% of pure *trans*-diol **21**. Deprotection of the acetonide afforded (±)-conduritol C. The overall yield from commercially available cyclohexadienediol **19** was 54%.



Scheme 12

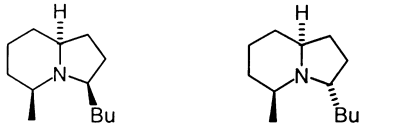


Scheme 13

Enantiomerically pure (+)- and (–)-conduritol C were obtained via enzymatic hydrolysis of the diacetate **20**. The enzymatic hydrolysis was highly efficient and gave 49% of the enantiomerically pure diol together with 48% of enantiomerically pure diacetate. In both cases the enantiomer excesses were >99.5%. Deprotection of the diol gave (–)-conduritol C and deprotection-hydrolysis of the (+)-diacetate gave (+)-conduritol C.

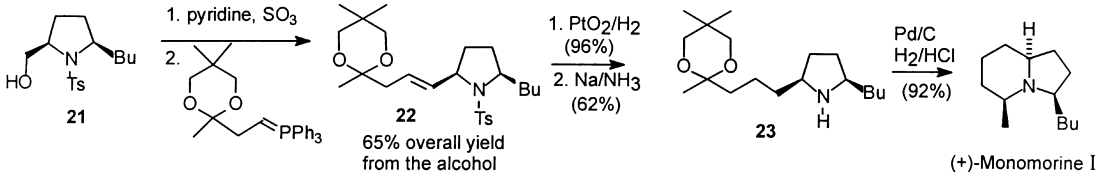
SYNTHESIS OF MONOMORINE I

Indolizidine alkaloids have attracted considerable interest recently due to their fascinating biological activity. Two of these alkaloids, monomorine I and indolizidine 195B (Scheme 14), have been popular targets for synthetic organic chemists. Monomorine I is a trail pheromome of the Pharaoh ant *Monomorium pharaonis L. To* control this ant by pheromone manipulation it is of interest to produce this compound via organic synthesis.



Scheme 14

The strategy for synthesis of (+)-monomorine I is based upon a previously published procedure for the synthesis of enantiomerically pure 2,5-disubstituted pyrrolidines [15]. Pyrrolidine **21** was obtained from Pdcatalyzed tosylamination of a 1-benzyloxy 2,4-diene monoepoxide to give a 5-tosylamino-3-alken-1,2-diol derivative followed by cyclization. Transformation of pyrrolidine **21** to monomorine I is shown in Scheme 15. Oxidation of pyrridylmethyl alcohol **21** to the aldehyde and subsequent coupling with the Wittig reagent from protected 4-bromo-2-butanone afforded compound **22** in 65% overall yield from the alcohol. Hydrogenation of the double bond and removal of the tosyl group afforded **23**. In the final cyclization the ketone is liberated, which undergoes a reductive amination to give monomorine I in 92% yield.



Scheme 15

ACKNOWLEDGEMENTS

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