Synthesis of natural products via stereocontrolled palladium-catalyzed reactions*

Jan-E. Bäckvall

Department of Organic Chemistry, Arrhenius Laboratory, Stockholm University, SE-106 91 Stockholm, Sweden

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 functionalization 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].

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 of the aminoalcohol derivative, e.g. the amino and oxygen groups can be introduced in either a cis or trans fashion.

Scheme 2

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 aryl dienes were prepared according to that method or via Grignard addition to 2-cyclohexenone and subsequent elimination. Palladium-catalyzed chloroacetoxycylation of 2-phenyl-1,3-cyclohexadiene afforded the chloro acetate in a highly stereo- and regioselective reaction in 62% yield (Scheme 3). The corresponding chloroacetoxycylation of the pyridyl derivative was also regio-and stereoselective but the yield was moderate (30%).

Further functionalization of the 2-phenyl-1,4-chloroacetate 1 is shown in Scheme 4. Palladium-catalyzed nucleophilic 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 SOC\textsubscript{1}\textsubscript{2} to give 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\textsubscript{N}2 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.
Finally, epibatidine was synthesized. (Scheme 6) [6]. The same strategy as for the synthesis of the exo-phenyl derivative \( \text{exo-6} \) was employed. Also in this case the hydrogenation was highly stereoselective.

\[
\begin{align*}
\text{Cl} & \quad \text{OAc} \\
\text{NHTs} & \quad \text{OMe} \\
\text{1. Pd}^0, \text{NaNH}_2 & \text{(79\%)} \\
\text{2. K}_2\text{CO}_3 & \text{OH} \\
\text{Cl} & \quad \text{MeOH/H}_2\text{O} \\
\text{K}_2\text{CO}_3 & \text{(63\%)} \\
\text{1. Pd}^0, \text{NaNH}_2 & \text{(79\%)} \\
\text{2. K}_2\text{CO}_3 & \text{OH} \\
\text{Cl} & \quad \text{MeOH/H}_2\text{O} \\
\text{K}_2\text{CO}_3 & \text{(63\%)} \\
& \quad \text{SOCl}_2 \\
& \quad \text{(65\%)} \\
\end{align*}
\]

Scheme 6

SYNTHESIS OF PACONILACTONES

In traditional Japanese and Chinese medicine Paeony root (\( \text{Paeoniae Radix} \)) 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 enantiomerically 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 enantiomerically pure acid \( 10 \) in 77\% yield as a 1:1 epimeric mixture.

\[
\begin{align*}
\text{Me} & \quad \text{H} \\
\text{O} & \quad \text{Me} \\
\text{Me} & \quad \text{H} \\
\text{O} & \quad \text{Me} \\
\text{Me} & \quad \text{O} \\
\text{Me} & \quad \text{H} \\
\text{O} & \quad \text{Me} \\
\text{Me} & \quad \text{O} \\
\end{align*}
\]

\( Paeonilactone \ A \)

\( Paeonilactone \ B \)

\( Paeonilactone \ C \)

Scheme 7

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 \( \text{Pd(OAc)}_2 \) 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 \( \text{et al.} \) [11] (Scheme 9).

\[
\begin{align*}
\text{OH} & \quad \text{Me} \\
\text{O} & \quad \text{Me} \\
\text{OH} & \quad \text{Me} \\
\text{O} & \quad \text{Me} \\
\text{OH} & \quad \text{Me} \\
\text{O} & \quad \text{Me} \\
\text{OH} & \quad \text{Me} \\
\text{O} & \quad \text{Me} \\
\end{align*}
\]

\( Paeonilactone \ A \)

\( Paeonilactone \ B \)

\( Paeonilactone \ C \)

Scheme 8

\( Paeonilactone \ A \)

\( Paeonilactone \ B \)

\( Paeonilactone \ C \)

Scheme 9

©1999 IUPAC, Pure Appl. Chem. 71, 1065–1070
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 triflate 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**

**SYNTHESIS OF CONDURITOL C**

Conduritols constitute a class of cyclohexenetetrole with interesting biological activity including antibacterial, 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 pheromone 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](image1)

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 Pd-catalyzed 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](image2)

ACKNOWLEDGEMENTS

I wish to express my sincere appreciation to my co-workers whose names appear in the reference list, for their efforts in exploring the chemistry outlined in this review. Financial support from the Swedish Natural Science Research Council and the Swedish Research Council for Engineering Sciences is gratefully acknowledged.

REFERENCES


©1999 IUPAC, Pure Appl. Chem. 71, 1065–1070

(a) C. Broka. *Med. Chem. Res.* **4**, 449 (1994); this review describes 9 total syntheses until September 1994. (b) For more recent work see references cited in [6].


S. W. Riesinger, J. Löfstedt, J.-E. Bäckvall. Submitted for publication.