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Palladium (II) catalyzed 5-*endo* epoxynitrile cyclizations: total syntheses of enokipodins A and B

Jesús Armando Luján-Montelongo, José G. Ávila-Zárraga *

Facultad de Química, Universidad Nacional Autónoma de México, D.F., 04510, Mexico

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ABSTRACT

New total syntheses of the cuparenic sesquiterpenes enokipodins A and B were accomplished. The key step involves a novel, cationic-controlled and palladium (II) improved, 5-*endo* cyclization of an α-aryl-δ-epoxynitrile. The cyclization occurs with unmatched regioselectivity and high stereoselectivity. The synthesis is completed in 5 steps achieving yields of 50% for enokipodin A and 55% for enokipodin B.

Enokipodins A–D (**1**–**4**) are four cuparenic sesquiterpenes isolated from the edible mushroom *Flammulina vellutipes* (Enokitake) by Ishikawa et al.[1] From this specie, a variety of compounds with pharmacological activity have been isolated.[2] Being structurally similar to coprinol[3] (**5**) and lagopodin A[4] (**6**) (Fig. 1), in terms of their polycyclic skeleton, enokipodins show similar biological activity against the *Gram*-positive bacteria *Bacillus subtilis* and *Staphylococcus aureus*;[1,3,4] however, they were ineffective against Gram-negative bacteria.[3]

It's been recognized that cuparenic sesquiterpenes are interesting synthetic targets[5–9] due to the difficulty on constructing the quaternary carbon centers over the cyclopentane moiety. Concerning the stated above, enokipodins A–B (**1**–**2**) have been attractive to screen diverse methodologies intended to build cyclopentanic systems[9a–c] as well as the application of asymmetric building protocols for benzylic centers.[9d–f] There is no doubt enokipodins have been the most recurring synthetic targets among all the oxidized cuparenic species.

Although the *RCM*,[5] dicarbonyl compound intramolecular condensation[6] and cyclobutane rearrangment[7] are frequently chosen as cuparene-type sesquiterpene syntheses methodologies, the intramolecular nucleophilic displacement[8] hasn't been a widely accepted approach to assemble the cyclopentane system on those compounds. As expected, the enokipodin's five-membered system is mainly synthesized by the first three approaches only.[9]

Recently, we reported a study regarding the cyclization of α-aryl-δ-epoxynitrile type compounds featuring a novel cationic metal regioselectivity control.[10] This type of regiocontrol is barely known;[11] however, an analogous control has been found in reactions which show divergence in their stereoselectivity by the involvement of different alkaline cations.[12] It was found the use of lithium or potassium salts of the hexamethyldisilamide base in these systems, employing high boiling point hydrocarbonated solvents, promote a 5-*endo* pathway of cyclization; on the other hand, sodium hexamethyldisilamide in low boiling hydrocarbonated solvents leads to 4-*exo* cyclizations. Therefore, it could be proposed the *Stork* cyclization (Scheme 1)[13] could be applied not only in constructing cyclobutane-containing molecules originally stated by the author, but to species which include cyclopentanic rings like cuparenic derivatives as well.

These results established that *Lewis' acids* involved in these systems had an important effect in terms of reaction regioselectivity which could be directly translated to control the carbocycles proportion in the product mix. This is a complementary work to previous studies where the cyclization preferred pathway was attributed just to the reagent's sterical profile,[13,14] and became possible the regiochemical outcome modification by modulating experimental conditions and base.

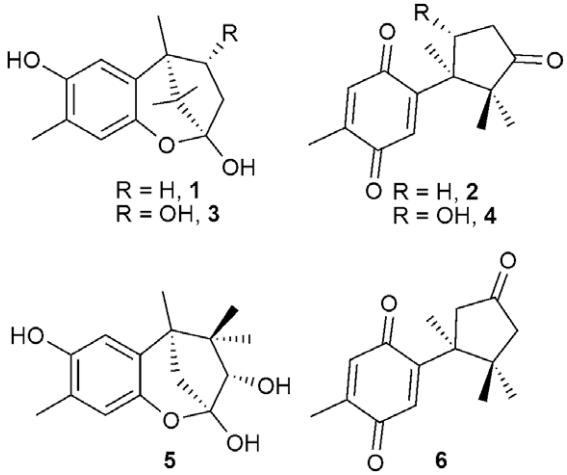

Figure 1. Enokipodins A–D (**1**–**4**) and some related oxidized cuparenic species.

* Corresponding author. Tel.: +525 556 223 784; fax: +525 556 223 722.
E-mail address: gavila@correo.unam.mx (J.G. Ávila-Zárraga).

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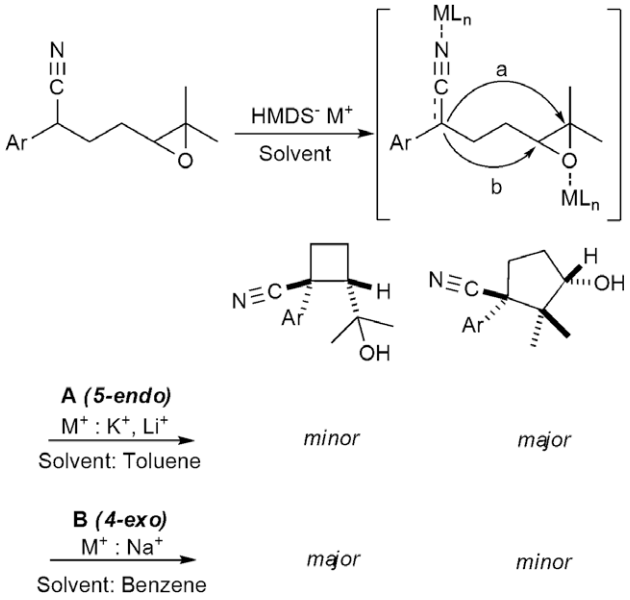
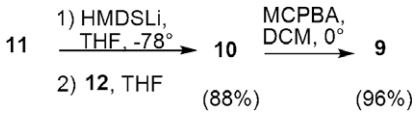


Scheme 1. Cation controlled regioselective cyclizations of α-aryl-δ-epoxynitriles.

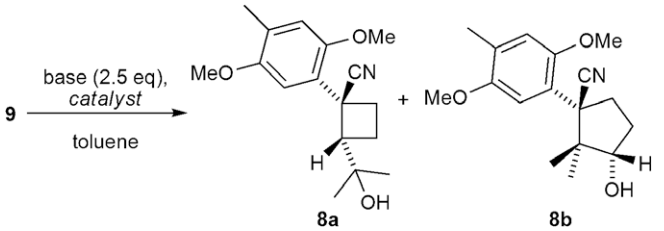
Keeping this in mind we decided to include in this type of cyclization other acidic species, in order to evaluate if an additional 5-*endo* promotion could emerge to improve yield of cyclopentanic structures over cyclobutanic with no chemo and stereoselectivity sacrifice whatsoever. In that way, we developed a new divergent route towards the enokipodins A and B (**1**, **2**) total syntheses by employing a methodology based on intramolecular nucleophilic carbocyclization of an α-aryl-δ-epoxynitrile which features high regioselectivity by alkaline metal cationic modulation, assisted by additional *Lewis* acids.

Scheme 2 depicts the retrosynthetic plan for Enokipodins A and B (**1**, **2**). It was expected that cyclopentanone **7** could be precursor



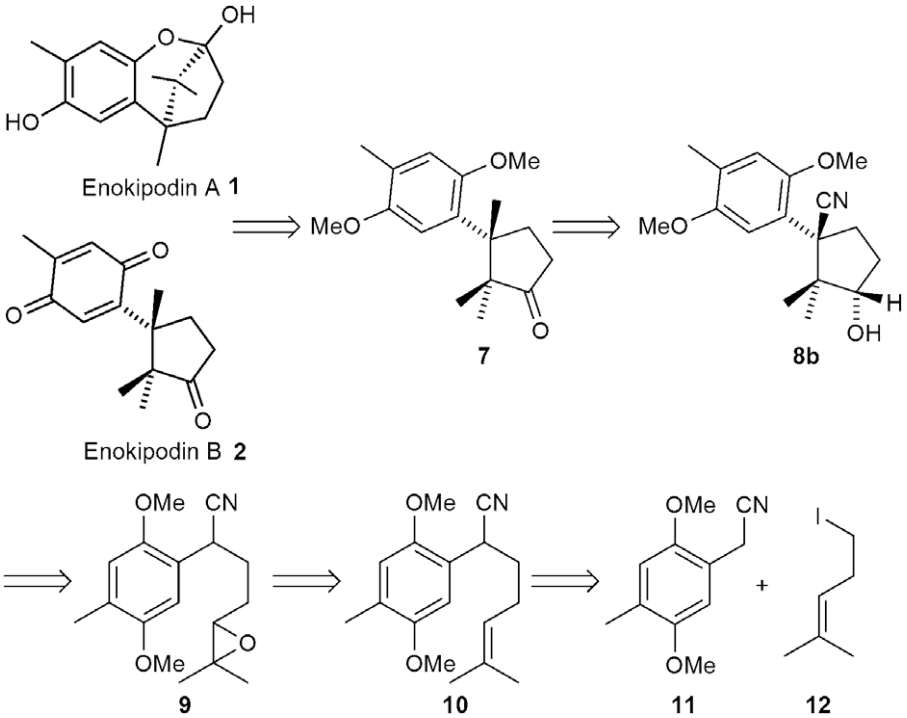
Scheme 3. Synthesis of the δ-epoxynitrile **9**.

Table 1
Lewis acid catalyzed δ-epoxynitrile **9** anionic cyclization study



Entry	Base	Catalyst	Cat. load (% mol)	Yield[a] (%)	**8a**:**8b**[b]
1	KHMDS	—	—	90	2.8:1
2	KHMDS	$Ti(OiPr)_4$	20	20(60)	2.9:1
3	KHMDS	$InCl_3$	20	79	1:2.1
4	KHMDS	$Cu(OTf)_2$	20	60	1:4.9
5[c]	KHMDS	$Cu(OTf)_2$	20	74	3:1
6	KHMDS	BiI_3	20	27	2.2:1
7	KHMDS	$Bi(OTf)_3$	20	0(100)	—
8	KHMDS	$Sc(OTf)_3$	20	19	3.7:1
9	KHMDS	$PdCl_2$	20	65	1:4.8
10[c]	KHMDS	$PdCl_2$	20	79	3.2:1
11	KHMDS	$PdCl_2$	10	80	1:4.7
12	KHMDS	$PdCl_2$	5	85	1:4.9
13	DIPEA	$PdCl_2$	10	0(100)	—
14	—	$PdCl_2$	10	0(100)	—
15	LHMDS	$PdCl_2$	5	80	1.2:1

[a] Parentheses indicate the recovered yield of epoxynitrile **9**.
[b] Determined by ^1H NMR of the crude product.
[c] In these cases benzene was used as solvent.



Scheme 2. Retrosynthetic plan for the enokipodins syntheses.

of **1** and **2**, as described by Srikrishna.[9a] Key intermediate **9** synthesis was conducted as shown in Scheme 3. Starting from 2,5-dimethoxy-4-methylphenyl acetonitrile[10,15] (**11**), homoisoprenilic oxide moiety was constructed by an alkylation–oxidation protocol.[10]

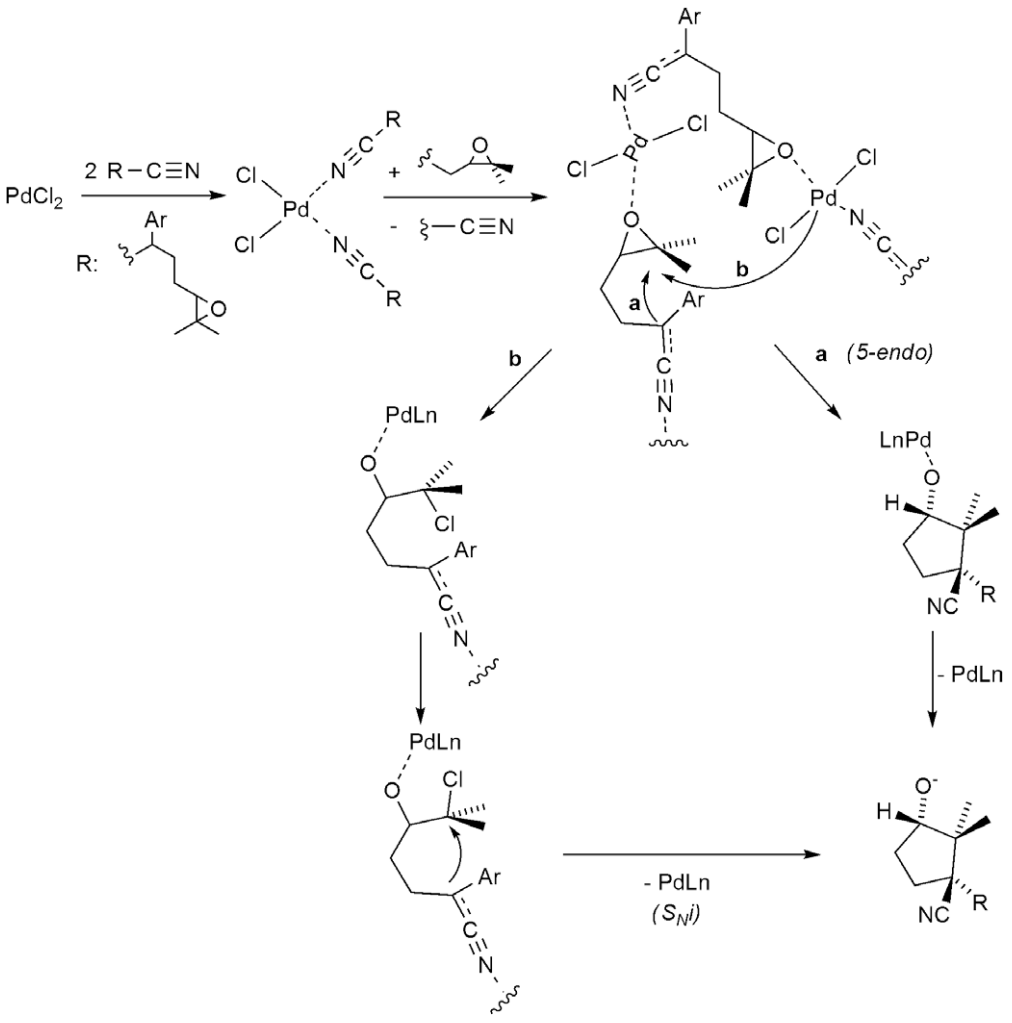
With δ-epoxynitrile **9** on hand, we looked for the regioselectivity improvement of its cyclization by adding *Lewis acids* (Table 1). Considering epoxynitrile cyclization, comparable in some way to an intramolecular aldolic reaction, applied criteria attempted to mimetize these species catalytic role, especially on Pd(II),[16] Cu(II),[17] Ti(IV),[18] Sc(III),[19] In(III)[20] y Bi(III)[21] cases. Furthermore, some of these metals are involved in epoxide catalytic openings.[22]

As shown on Table 1, both $PdCl_2$ (entry 9) and $Cu(OTf)_2$ (entry 4) are outstanding catalysts to enhance regioselectivity when the reaction was carried out with KHMDS in toluene (which showed best results at the absence of any additive). However, the reaction where Pd (II) took part, showed the best yield as well as a "cleaner" profile (entry 9). Once the appropriate catalyst was selected, the best result was achieved with a 5% mol of $PdCl_2$ (entry 12), which kept good regioselectivity and slightly improved yield. As we anticipated, reactions in benzene didn't show preference on the 5-*endo* pathway (entries 5 and 10).

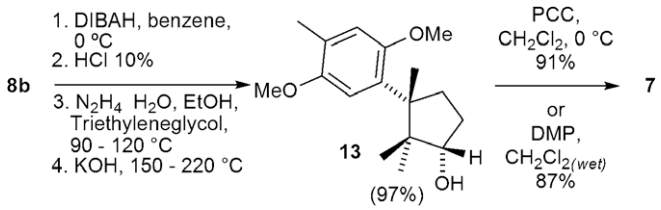
5-*Endo* promotion effected by $PdCl_2$ can be understood by inspecting two presumably side effects (Scheme 4). First, $PdCl_2$ could be forming a coordination entity, where nitrogen of the *cyano* function could participate in the metallic core, in such way that a rearrangement would take place into, changing from an *N*-coordinated to *O*-coordinated specie. At this point, once activated the oxiranyl function and promoting the C–O bond weakening of the more substituted carbon, 5-*endo* pathway would be accessible. Alternatively, regiospecific formation of a chlorohydrin intermediate[23] could take place, fixing the reactive position on the more substituted carbon. Interestingly, usage of lithium base showed poor regioselectivity (Table 1, entry 15) and usage of DIPEA or absence of base afforded no cyclization products (Table 1, entries 13 and 14). This way, it was established that both base nature and metallic counter-ion are essential to achieve good regioselectivity.

Important to mention *Lewis* acid catalized cyclization is completely stereoselective; this was concluded by inspecting ^{1}H NMR, ^{13}C NMR and GC/EIMS spectra on both regioisomers. The cyclopentanic isomer relative stereochemistry (**8b**) was assigned as *like* by means of NOESY experiments (vide infra).

Next step involved the reduction of *cyano* to *methyl* and oxidation of *hydroxyl* group of the cyclopentane moiety (Scheme 5). At first step, cyanocyclopentyl alcohol **8b** was treated with DIBAH (along with the corresponding acidic workup) affording an aldehyde derivative which was used with no further purification in the next step. The Huang-Minlon[24] procedure applied to the residue yields the reduced cyclopentanol **13** in an outstanding yield (2 steps, 97%). Later on, cyclopentenone **7** was obtained in 87% yield by Dess–Martin[25] oxidation of **13**, which was slightly inferior but less harmful to the environment compared to PCC oxidation (91%).[26]



Scheme 4. Possible pathways of $PdCl_2$ assisted 5-*endo* cyclization of **9**.



Scheme 5. Preparation of precursor **7**.

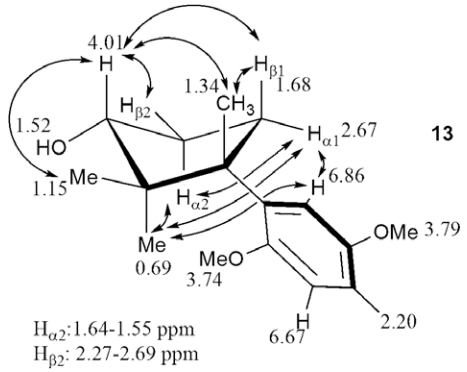
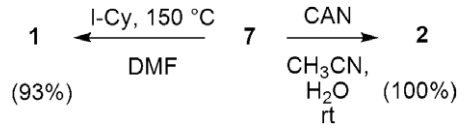


Figure 2. Relevant NOE correlations of **13**.



Scheme 6. Final steps on enokipodins A and B (**1**, **2**) syntheses.

It's remarkable the exhaustive reduction effected by the DIBAH - Huang-Minlon sequence doesn't epimerize any stereogenic center as confirmed by 1D NMR and NOESY experiments (Fig. 2).

Having enokipodin's precursor **7** available, we proceed with the enokipodin B (**2**) synthesis final step by oxidative cleavage using CAN. The yield is excellent, almost identical to results shown by Srikrishna[9a] and Kuwahara.[9d] On the other hand, the acidic cleavage-cyclization of **7** was carried out employing cyclohexyl iodide,[27] allowing the access to enokipodin A (1) in good yield (93%).

In conclusion, we have accomplished enokipodins A and B syntheses by employing a cation-controlled regioselective ring opening of a tertiary epoxynitrile which follows predominantly a 'non-favored' palladium-catalyzed 5-*endo pathway*. As catalyst, $PdCl_2$ has proved to be suitable to enhance regioselectivity; however, other *Lewis* acids such as $Cu(OTf)_2$ can be useful as well. Although it was proposed a tentative explanation in regards the achieved high regioselectivity at the key step, other effects could be involved in the process as shown within the additional experiments where other bases were employed. As spectroscopic analyses revealed, cyclization occurs with high diasteroselectivity; therefore, this methodology would provide a synthetic tool for stereoselective generation of two contiguous quaternary centers (Scheme 6).

Acknowledgments

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Supplementary data

Supplementary data (experimental procedures and spectral data for compounds **1**–**2**, **7**, **8a**–**b**, **13**) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.02.072.

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