Pergamon

Tetrahedron Letters 42 (2001) 589–592

TETRAHEDRON LETTERS

Stereoselective dihydropyrido(2,1-*a*)isoindolone synthesis via diastereodivergent Heck cyclisations on chiral 1,4-dihydropyridines†

Christophe Pays and Pierre Mangeney*

Laboratoire de Chimie des Organo-Eléments associé au CNRS, Université P. et M. Curie, 4, Place Jussieu, F-75252 Paris Cedex 05, France

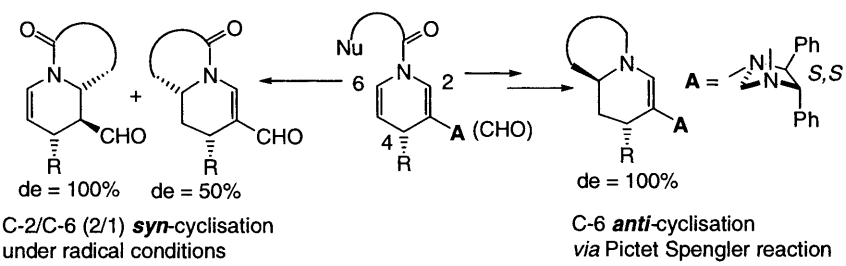
Received 10 October 2000; accepted 7 November 2000

Abstract—A stereoselective dihydropyrido(2,1-*a*)isoindolone synthesis is described via diastereodivergent cyclisations by using reductive or non-reductive Heck reactions on chiral 1,4-dihydropyridines.

We have already disclosed the synthesis of polycyclic nitrogen heterocycles by regio- and diastereoselective cyclisations of chiral *N*-acyl-1,4-dihydropyridines according to Scheme 1.

As shown below, a *syn* (compared to the C-4 substituent) cyclisation onto the C-2 or C-6 was observed under radical conditions, while an *anti* cyclisation onto the C-6 was obtained via a Pictet–Spengler reaction.[1] As part of our effort to extend the synthetic potentiality of such 1,4-dihydropyridines, we decided to study the possibility of a stereoselective synthesis of the isoindolone[2] ring system from **I** (C_4-(*R*), Scheme 2), using a Heck cyclisation.[3] If the cyclisation is regioselective onto the C-6–C-5 double bond (e.g. the less substituted one) and according to the two possible stereochemistries (*syn* or *anti*, Scheme 2), we could obtain the two diastereomeric intermediates **II** (*syn*) or **III** (*anti*). In **II** there is no possibility of *syn* β-elimination of XPdH therefore a tandem cyclisation–hydride capture[4] would give the [C_4-(*R*), C_6-(*R*)] adduct **IV**. If the cyclisation was to occur in an *anti* manner affording **III**, a *syn* β-elimination would give **VI** and then the [C_4-(*S*), C_6-(*S*)] adduct **VII** via a diastereoselective (*anti*) hydrogenation. An hydride capture performed, if it is possible, on **III** would give the [C_4-(*R*), C_6-(*S*)] adduct **V**. According to these possibilities, as shown in Scheme 2, three different diastereomers could be obtained. We wish to report here the results obtained during this study.

The dihydropyridine **1** was prepared, in 85% yield and 95% de, from the aminal **2** (*S*,*S*) by addition of MeCu in the presence of 2-iodobenzoyl chloride. An acidic hydrolysis afforded the aldehyde **3** (Scheme 3).[1]



Scheme 1.

Keywords: dihydropyridines; Heck reaction; isoindolone synthesis.

* Corresponding author. Tel.: +01 44 27 55 68; fax: +0144277567; e-mail: mangeney@moka.ccr.jussieu.fr

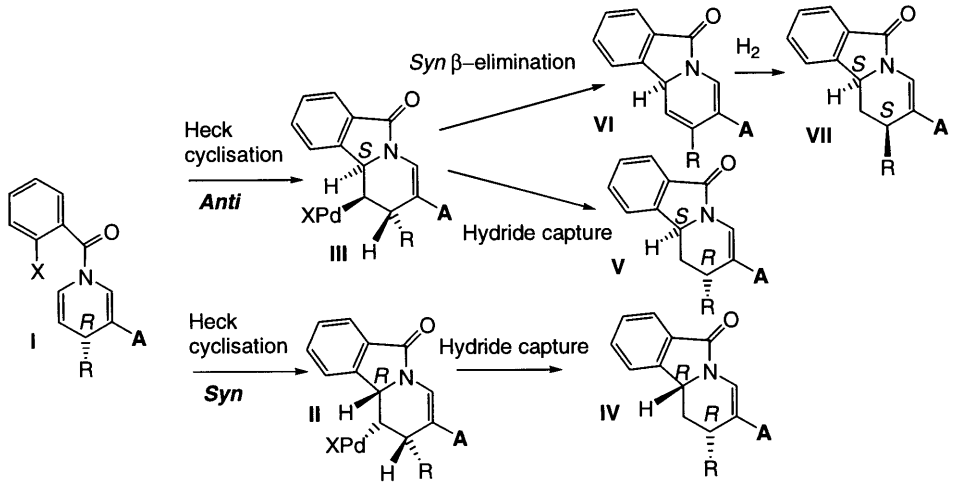
† Dedicated to Professor J. Normant on the occasion of his 65th birthday.

0040-4039/01/$ - see front matter
PII: S0040-4039(00)02010-4

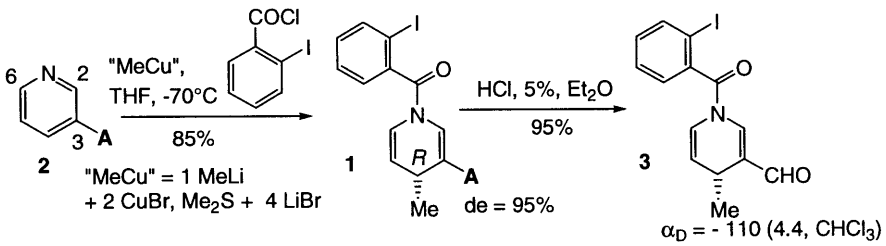
In the presence of a catalytic (5%) amount of $Pd(OAc)_2$, AcOK in DMF (90°C, 2h)[5] the dihydropyridine **1** was regioselectively converted into **4** (60% yield, 95% de, ^1H/NMR). The absolute configuration of this compound was determined by X-ray analysis[6] (Fig. 1) and found to be C-6(*S*). Therefore, **4** resulted from an *anti* carbopalladation then a *syn* β-elimination and an isomerisation of the double bond. Acidic hydrolysis of the aminal group in **4** afforded the aldehyde **5** (90% yield).

A tandem cyclisation–hydride capture performed on **1**, in the presence of 5% of $Pd(OAc)_2(PPh_3)_2$ and piperidinium formate, gave the two diastereomeric products **6** (94% de) and **7** (95% de) in a 7/3 ratio. These two compounds were separated by chromatography.

The *cis* relationship for the C_6-H and the C_4-Me substituents in **6** was determined by ^1H NMR (NOE, Scheme 4). Aminals **6** and **7** were respectively converted into the aldehydes **8** and **9** by acidic hydrolysis. The relative configuration of **9** was determined by chemical correlation from **10**, which was obtained by a diastereoselective hydrogenation on the less hindered face of **5** (Scheme 5).



Scheme 2.



Scheme 3.

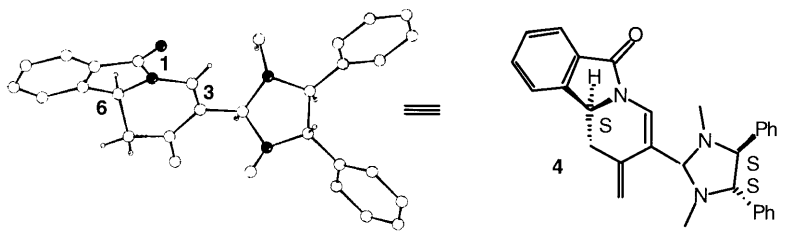


Figure 1.

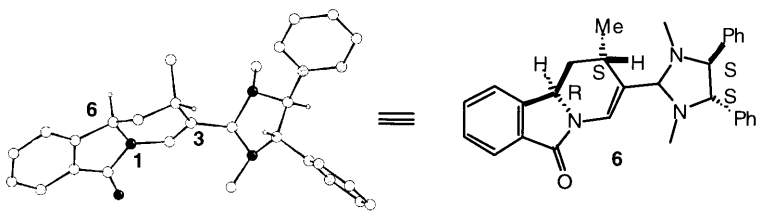
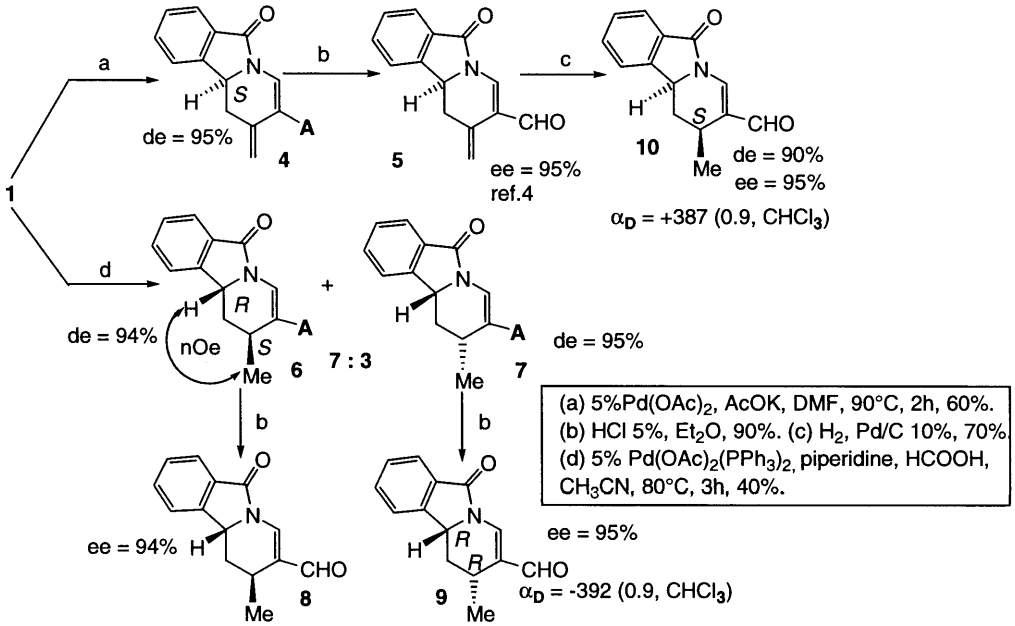
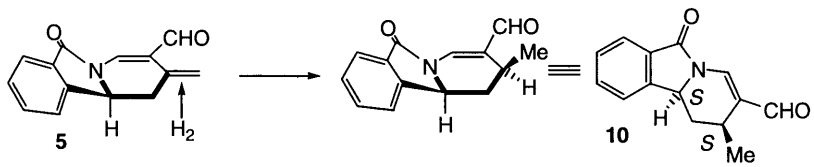


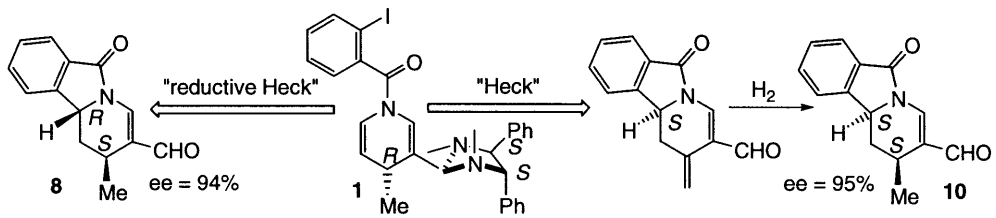
Figure 2.



Scheme 4.



Scheme 5.



Scheme 6.

The ^{1}H NMR spectra of **9** and **10** were identical, but different from the ^{1}H NMR of **8**. Therefore, since **8** was obtained from **6** (*cis* relationship for C_6-H and C_4-Me), we postulate that the C_6-H and C_4-Me relationship in **9** and **10** was *trans*. Surprisingly, the signs of their optical rotation were opposite, showing that these two products were enantiomers. The absolute configuration of **6** was determined by X-ray analysis[6] (Fig. 2) and found to be C-4(*S*) and C-6(*R*). Therefore the two diastereomers **6** and **7**, obtained by a tandem cyclisation–hydride capture, were the result of a *syn* carbopalladation and a partial epimerisation of the C-4 methyl group.

In conclusion, the cyclisation occurs selectively onto the C-5–C-6 double bond, but the stereochemistry is strongly dependent on the reaction conditions. As summarized in Scheme 6, starting from the same dihydropyridine **1**, it is possible to prepare selectively the dihydropyridoisoindolones **8** or **10** having, respectively, the *R*,*S* and *S*,*S* configurations, with ee = 94% and 95%, by using non-reductive or reductive Heck cyclisations. Such a result was totally unexpected and detailed mechanistic considerations will be reported in due course. Nevertheless, it seems synthetically useful to be able to change the stereochemistry of an intramolecular Heck reaction.

References

1. Mangeney, P.; Gosmini, R.; Raussou, S.; Commerçon, M.; Alexakis, A. *J. Org. Chem.* **1994**, *59*, 1877–1888. Mangeney, P.; Hamon, L.; Raussou, S.; Urbain, N.; Alexakis, A. *Tetrahedron* **1998**, *54*, 10349–10362
2. Hunter, R.; Richards, P. *Tetrahedron Lett.* **2000**, *41*, 3755–3758.
3. For recent reviews and some new related papers see: Negishi, E. I.; Coperet, C.; Shengming, M.; Show-Yee, L.; Fang, L. *Chem. Rev.* **1996**, *96*, 365–393. Heumann, A.;

Réglier, M. *Tetrahedron* **1996**, *52*, 9289–9346. Cabri, W.; Candiani, I. *Acc. Chem. Res.* **1995**, *28*, 2–7. Friestad, G. K. Branchaud, B. P. *Tetrahedron Lett.* **1995**, *36*, 7047–7050. Pigeon, P.; Decroix, B. *Tetrahedron Lett.* **1996**, *37*, 7707–7710. Comins, D. L.; Joseph, S. P.; Zhang, Y. *Tetrahedron Lett.* **1996**, *37*, 793–796. Shibasaki, M. D. J.; Boden, C.; Kojima, A. *Tetrahedron* **1997**, *53*, 7371–7395. Bombrun, A.; Sageot, O. *Tetrahedron Lett.* **1997**, *38*, 1057–1060. Kirschbaum, S.; Waldmann, H. *J. Org. Chem.* **1998**, *63*, 4936–4946. Ripa, L.; Hallberg, A. *J. Org. Chem.* **1997**, *62*, 595–602. Diaz, P.; Gendre, F.; Stella, L.; Charpentier, B. *Tetrahedron* **1998**, *54*, 4579–4590. Birman, V. B.; Rawal, V. H. *Tetrahedron Lett.* **1998**, *39*, 7219–7222. Han, X.; Larock, R. C. *Synlett* **1998**, 748–750. Söderberg, B. C.; Rector, S. R.; O'Neil, S. N. *Tetrahedron Lett.* **1999**, *40*, 3657–3660.

4. Burns, B.; Grigg, R.; Sridharan, V.; Worakun, T. *Tetrahedron Lett.* **1988**, *29*, 4325–4328. Friestad, G. K.; Branchaud, B. P. *Tetrahedron Lett.* **1995**, *36*, 7047–7050.
5. Cacchi, S.; Ciattini, P. G.; Morera, E.; Pace, P. *Synlett* **1996**, 545–546.
6. Crystallographic data have been deposited at the Cambridge Crystallographic Data Centre (no CCDC 150466).