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Tetrahedron Letters 45 (2004) 9003–9006
Tetrahedron Letters

Short diastereoselective synthesis of *cis*- and *trans*-hexahydropyrido[2,1-*a*]isoindole derivatives

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Received 6 September 2004; revised 8 October 2004; accepted 8 October 2004
Available online 22 October 2004

Abstract—A new and highly stereoselective access to 4,10b-*trans* or 4,10b-*cis* hexahydropyrido[2,1-*a*]isoindole derivatives is reported, both requiring an intramolecular Mannich-type reaction as key step. The *cis* diastereoisomer is obtained in three steps from a 2-alkyl benzaldehyde through the stereoselective formation of a 2,6-*cis*-disubstituted piperidine, while the *trans* stereomer is efficiently obtained, in a single step, if a 2-formyl benzoic acid is involved in the Mannich cyclization process.

The dihydroisoindolin-1-one ring system is present in numerous synthetic and natural compounds, which exhibit interesting biological properties. For example, 3-substituted dihydroisoindolin-1-ones such as pazinaclone **1**[1] and zoplicone **2**[2] possess a pharmaceutical profile similar to benzodiazepines (sedatives, hypnotics)[3] and have been commercialized as anxiolytics. Fused polycyclic dihydroisoindolin-1-ones have also been reported, such as lennoxamine **3**[4] (isolated from *Berberis darwinii*) or compound **4**,[5] which has been described as a non-nucleosidic HIV reverse transferase inhibitor (Fig. 1).

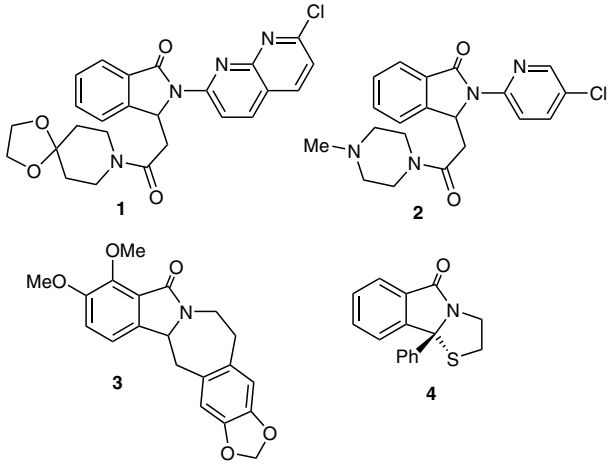

Figure 1.

If several synthetic pathways have been proposed to obtain 3-substituted dihydroisoindolin-1-ones[6], only a few were devoted to the asymmetric synthesis of such framework,[7] starting either from phthalimide derivatives or from 2-formyl benzoic acid. Consequently, new stereoselective routes to dihydroisoindolin-1-ones have to be explored. Part of our research program concerns asymmetric synthesis of saturated *N*-heterocycles and we have recently proposed a stereoselective access to polysubstituted piperidine systems. Our approach, summarized in Scheme 1, rests on the use of an aldehyde involved in a Mannich-type reaction with an α-chiral ketoprotected 1,3-aminoketone **5** and gives a selective access to the corresponding *cis*-2,6-disubstituted piperidines.[8] This methodology has been successfully applied to the synthesis of natural products.[9]

Accordingly, we reasoned that this strategy, applied from 2-formylbenzoic acid and derivatives, should furnish a rapid stereoselective entry to the hexahydropyrido[2,1-*a*]isoindolinone ring system via cyclization of the piperidine intermediate **6** (Scheme 1). In order to verify the feasibility of this sequence, preliminary experiments were carried out using simplest non-chiral keto protected β-aminoketone **7**.[10] Thus, we could observe

Keywords: Isoindoles; Piperidines; Stereoselective synthesis; Intramolecular Mannich reaction.
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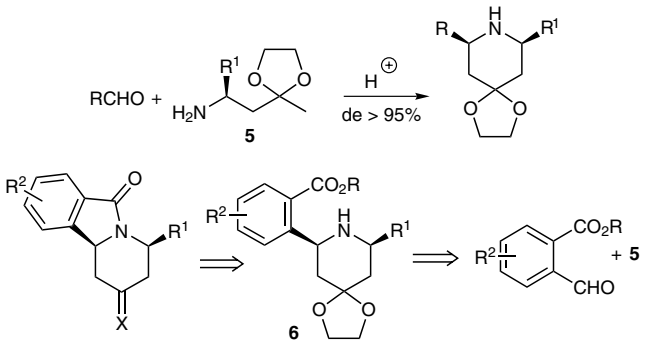
doi:10.1016/j.tetlet.2004.10.045

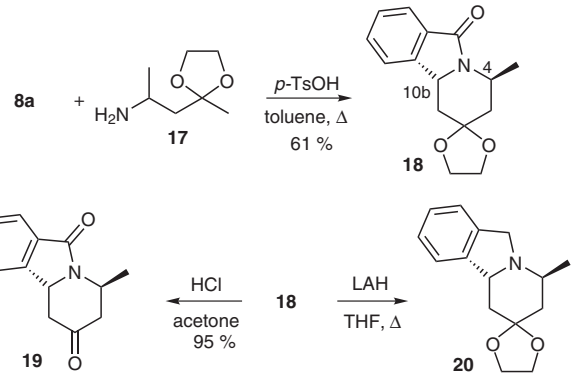


Scheme 1.

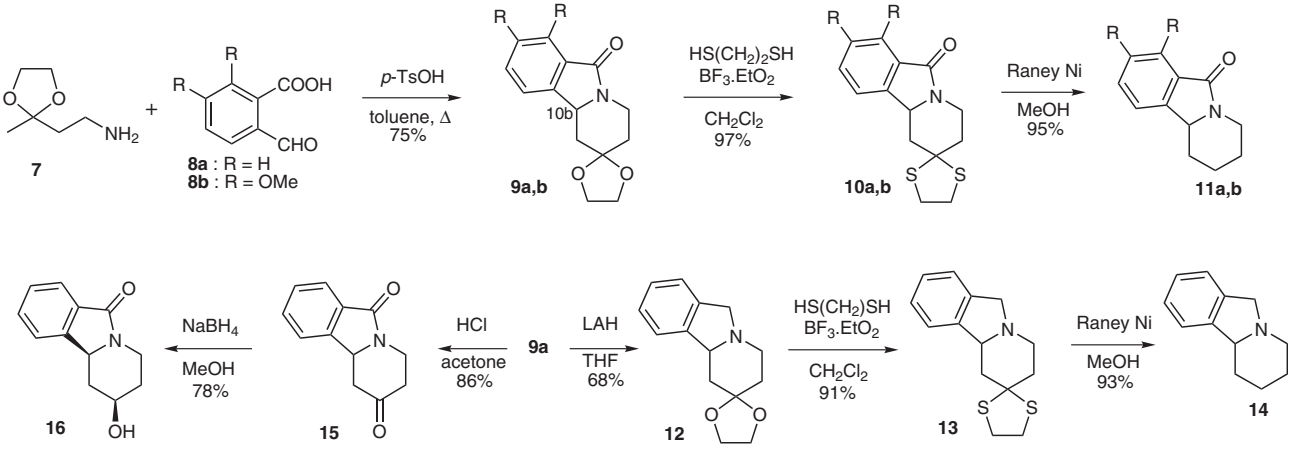
that condensation of 2-formyl benzoic acids **8a**,**b** with amine **7**, in toluene at reflux in the presence of *para*-toluenesulfonic acid (1.2 equiv), gave directly tetracyclic lactams **9a**,**b** as sole reaction products (75% isolated yield; Scheme 2). Structures of **9a**,**b** were unambiguously deduced from ^{1}H NMR data, notably with the H-10b signals (dd, $J = 5.5$ and 12.5 Hz) characterizing a *pseudo* axial position. Subsequent treatment of **9** with an excess of ethanedithiol in dichloromethane in the presence of $BF_3{\cdot}Et_2O$ afforded in nearly quantitative yields dithiolane derivatives **10a**,**b** whose hydrogenolysis was completely and cleanly achieved, using W2 Raney nickel[11] in refluxing methanol, and furnished compounds **11a**,**b**. Spectral data of **11a** were identical in all respect with those previously described.[12] On the other hand, carboxamide LAH reduction of **9a** prior to the same deoxygenation sequence yielded efficiently polycyclic isoindole derivatives **12**–**14** (Scheme 2). Spectral data of **14** hydrochloride salt were in excellent agreement with those already reported.[13]

Moreover, standard deprotection of **9a** led to the parent 2-oxo compound **15** (86%) whose selective reduction, using $NaBH_4$ in methanol at room temperature, afforded in 78% yield equatorial 2-hydroxy derivative **16** as sole detectable (^{1}H NMR) diastereoisomer (Scheme 2). With these first results, we could demonstrate that intramolecular Mannich reaction constitutes a valuable tool for the rapid construction of a wide range of new fused polycyclic isoindoles.

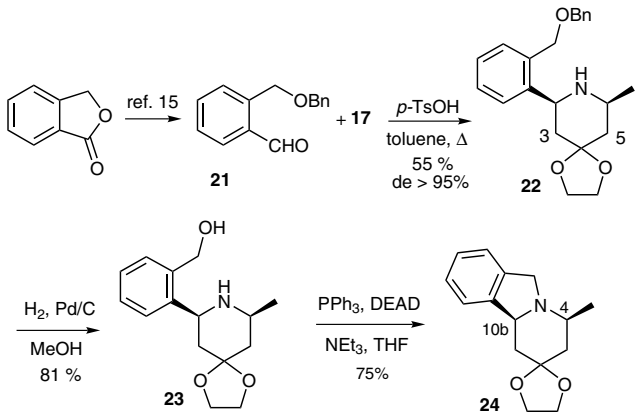
Next was the valuation of this approach in asymmetric synthesis. Thus, ketoprotected 1,3-aminoketone (±)-**17**[8] and 2-formyl benzoic acid **8a** were engaged in the cyclization step under identical conditions (Scheme 3). By this way, we could observe the formation of isoindolone derivative **18**, as a unique stereoisomer (61% isolated yield), which was easily deprotected or reduced to give compounds **19** and **20**,[14] respectively. Careful examination of spectroscopic data of **18** prompted us to assign the unexpected (Scheme 1) 4,10b-*trans* relative stereochemistry. Effectively, if H-10b NMR signal (4.67 ppm, dd, $J = 13.0$ and 4.0 Hz) showed clearly a pseudo-axial position, signal corresponding to H-4 (4.74 ppm, dedoubled quintet, $J = 7.0$ and 1.5 Hz) seemed to indicate a pseudo-equatorial orientation and, consequently, a *trans* relationship between these two protons. In order to verify the postulated stereochemistry of **18**–**20**, and according to our ability concerning the asymmetric synthesis of piperidines, we decided to prepare the *cis* diastereomer of **20** via the isolation of a stable *cis*-2,6-disubstituted piperidine intermediate, prior to the isoindole system formation. Such an approach required the use, as carbonyl partner in the Mannich reaction, of a benzaldehyde



Scheme 3.



Scheme 2.



Scheme 4.

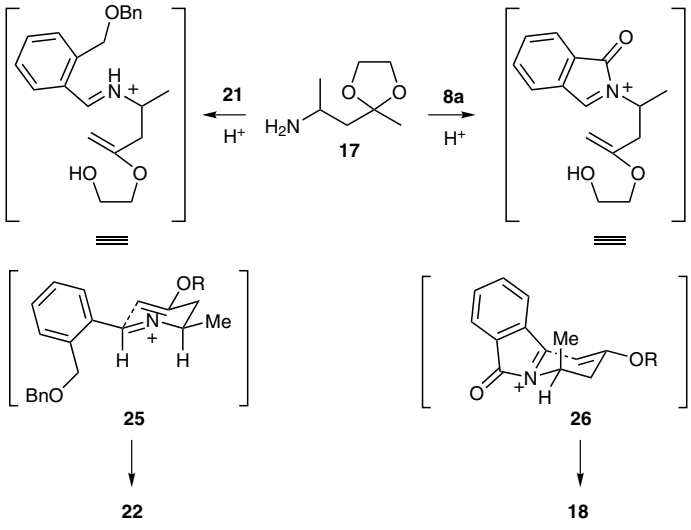
ortho-substituted by a group prohibiting the intramolecular lactam formation and allowing rapidly the last cyclization. For these reasons, 2-[(benzyloxy)-methyl]benzaldehyde **21**, conveniently prepared[15] in four steps from phthalide, was selected (Scheme 4). Thus, this compound reacted with amine **17** in the presence of 1.2 equiv of *para*-toluenesulfonic acid to yield (55%), as expected, *cis*-2,6-disubstituted piperidine **22** exclusively (Scheme 4).

Subsequent selective catalytic hydrogenolysis of **22** afforded piperidine **23** in 81% yield. Relative configurations of **22**–**23** were then unambiguously established from ^{1}H NMR spectra, particularly from the signals corresponding to axial H-3 and axial H-5, showing representative coupling constants for a 2,6-diequatorial disubstitution in a chair conformation. Finally, construction of the isoindole moiety was achieved using an intramolecular Mitsunobu reaction[16] and led to the expected 4,10b-*cis* tetracyclic compound **24**[14] in a 75% yield (Scheme 4). At this stage, direct comparison of spectroscopic data of **24** with those issued from product **20** (Scheme 3) showed, with no doubt, that these compounds are diastereoisomers, confirming here the 4,10b-*trans* relative stereochemistry of hexahydropyrido-isoindole derivative **20**.

In order to explain the stereochemical discrepancy observed between the two cyclization modes, giving **18** and **22**, some mechanistical aspects need to be pointed out.

If *cis*-2,6-disubstituted piperidine **22** is the normal cyclization product of the iminium ion **25** (Scheme 5) as demonstrated,[8] formation of *trans*-4,10b-isoindolone **18** proceeds obviously via an other intermediary specie. In this case, *N*-acyliminium ion **26** has to be considered. Effectively, and as already mentioned,[17,18] strong $A^{(1,3)}$ strain[19] orientates the conformational equilibrium of *N*-acyliminium **26** to the more stable conformer in which the methyl group occupies an axial position (Scheme 5). In consequence, intramolecular trapping of such an intermediate leads highly predominantly to the 4,10b-*trans* adduct **18**.

In conclusion, we have described herein a straightforward access to fused polycyclic isoindolinones. These compounds were obtained, in a single step, by acidic condensation of a ketoprotected-1,3-aminoketone and a 2-formylbenzoic acid. Furthermore, we could also demonstrate that, if a chiral aminoketone is involved, the reaction is highly diastereoselective, leading to the 4,10b-*trans* adduct as sole observable stereomer. Evidence of this configuration was unambiguously established through the highly stereoselective synthesis of a 4,10b-*cis* polycyclic isoindole compound, using as key intermediate a 2,6-*cis*-disubstituted piperidine prepared by intramolecular Mannich-type reaction. Our efforts are now devoted to the extension of these new routes to *cis* and *trans* hexahydro[2,1-*a*]isoindole derivatives to other aminoketones and aldehydes as well as their applications in the field of enantioselective synthesis. This crucial last point will permit, in particular, to precise all the mechanistical points of the 4,10b-*trans*-isoindolone



Scheme 5.

18 formation, and then to define the scope and the limitations of this process. Results will be published in due course.

Acknowledgements

We thank the Ministère de la Jeunesse, de l'Education Nationale et de la Recherche for financial support.

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14. Selected data for compounds **20** and **24**. **20**: (^{1}H NMR, 400 Mz, $CDCl_3$) δ (ppm): 7.2–7.0 (4H, m, aromatics); 4.35 (1H, d, J = 10,0 Hz, H-10b); 4.12 (1H, d, J = 13.0 Hz, H-6); 4.00–3.80 (5H, m, acetal and H-6); 3.25 (1H, hexplt, J = 6.5 Hz, H-4e); 2.10 (1H, dd, J = 13.0 and 2.0 Hz, H-1e); 1.95 (1H, dd, J = 13.0 and 5.0 Hz, H-3e); 1.80–1.75 (2H, m, H-1a and H-3a); 1.15 (3H, d, J = 6,5 Hz, CH_3). (^{13}C NMR, 100 Mz, $CDCl_3$) δ (ppm): 143.8; 139.5; 127.0; 126.8; 122.6; 121.5; 108.2; 64.3; 63.7; 58.8; 55.1; 50.1; 40.1; 16.1.
24: (^{1}H NMR, 400 Mz, $CDCl_3$) δ (ppm): 7.19–7.01 (4H, m, aromatics); 4.13 (1H, d, J = 12,0 Hz, H-6); 4.00–3.90 (4H, m, acetal); 3.63 (1H, d, J = 12,0 Hz, H-10b); 3.45 (1H, dd, J = 12.0 and 3.0 Hz, H-6); 2.75 (1H, m, H-4a); 2.22 (1H, dt, J = 12.0 and 3.0 Hz, H-1e); 1.70 (2H, m, H-1a and H-3e); 1.60 (1H, t, J = 13.0 Hz, H-3a); 1.14 (3H, d, J = 7,0 Hz, CH3).(^{13}C NMR, 100 Mz, $CDCl_3$) δ (ppm): 143.2; 139.9; 126.8; 126.7; 123.6; 121.4; 108.3; 65.0; 64.4; 64.1; 54.1; 53.6; 43.2; 38.0; 20.4.
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