ORGANIC LETTERS

2010
Vol. 12, No. 10
2178−2181

Straightforward Assembly of the Octahydroisoquinoline Core of Morphinan Alkaloids

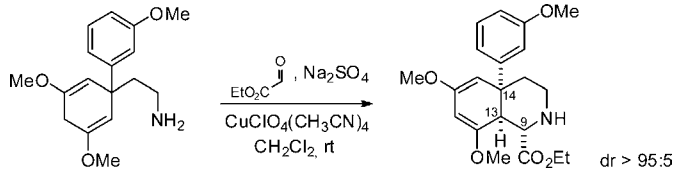
Julie Dunet, Raphaël Lebeuf, Gopal Bose, Frédéric Robert, and Yannick Landais*

Université de Bordeaux, Institut des Sciences Moléculaires, UMR-CNRS 5255, 351, cours de la libération, 33405 Talence cedex 05, France

y.landais@ism.u-bordeaux1.fr

Received February 24, 2010

ABSTRACT



The octahydroisoquinoline core of morphinan was assembled starting from readily available arylcyclohexadienes. Three different approaches were developed, including a metal- and an acid-mediated Mannich type process and an anionic-mediated cyclization. All provided the desired motif as a single diastereomer having a C9−C13−C14 *trans*−*cis* relative configuration.

The octahydroisoquinoline moiety **I** (in red, Figure 1) is a key component of the skeleton of naturally occurring alkaloids of *Papaver somniferum* including morphine **1**[1] and its closely related analogue pallidinine **2**, isolated from *Ocotea acutangula*. The highly functionalized aza-decaline core is substituted at C13 by an aromatic ring, leading to a *trans* (for **1**) or a *cis*-C−D-ring junction (for **2** and **3**), and possesses a quaternary center, for which installation is generally considered as the critical point in the synthesis of morphinan alkaloids.[1b] These biologically relevant compounds[2] have been assembled in a number of ways,[1,3] but their structural complexity still serves as the impetus for novel synthetic investigations. In the course of our ongoing research on the use of arylcyclohexadienes as a unified building block for the synthesis of amaryllidaceae, aspidosperma, and papaver alkaloids,[4] we recently focused our attention on the elaboration of the isoquinoline C−D rings of the morphinans.

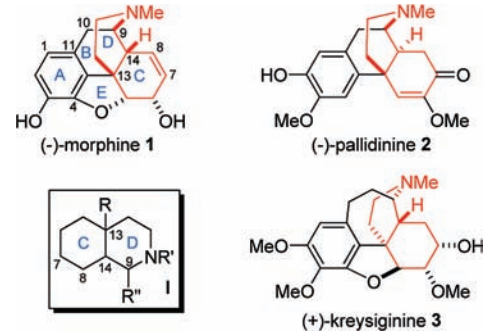


Figure 1. Isoquinoline moiety of morphinan alkaloids.

Cyclohexa-1,4-dienes have recently garnered a lot of attention, their desymmetrization offering an entry into a

(1) (a) Kutchan, T. M. *The Alkaloids: Chemistry and Biology*; Cordell, G. A., Ed.; Academic Press: London, 1998; Vol. 50, pp 257−316. (b) Blakemore, P. R.; White, J. D. *Chem. Commun.* **2002**, 1159–1168.

(2) Szántay, C.; Dörnyel, G.; Blaskó, G. *The Alkaloids: Chemistry and Pharmacology*; Cordell, G. A., Brossi, A., Eds.; Academic Press: London, 1994; Vol. 45, pp 128−222.

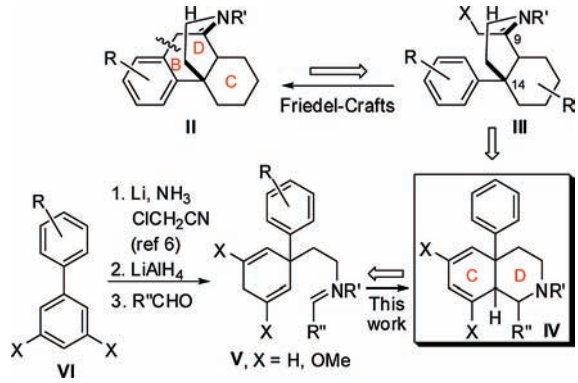
(3) (a) Zezula, J.; Hudlicky, T. *Synlett* **2005**, 388–405. (b) Taber, D. F.; Neubert, T. D.; Schlecht, M. F. *Strategies and Tactics in Organic Synthesis*; Harmata, M., Ed.; Academic Press: Oxford, 2004; Vol. 5, pp 353−389.

(4) (a) Beniazza, R.; Dunet, J.; Robert, F.; Schenk, K.; Landais, Y. *Org. Lett.* **2007**, *9*, 3913–3916. (b) Lebeuf, R.; Robert, F.; Schenk, K.; Landais, Y. *Org. Lett.* **2006**, *8*, 4755–4558, and references cited therein.

10.1021/ol1004627
Published on Web 04/21/2010

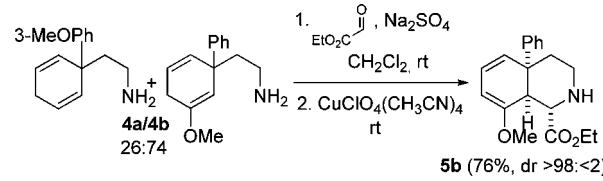
large variety of natural products and valuable intermediates.[5] We report herein our preliminary studies on the elaboration of the octahydroisoquinoline framework of isoquinoline alkaloids, using as key precursors, cyclohexadienes **V** (Scheme 1). These building blocks constitute valuable motifs for the construction of aza-decaline **IV** as the quaternary center bearing the aryl ring, and the ethylamino chain of targets **1**−**3** is already installed. Further stereocontrolled reactions on the cyclohexadiene moiety should concomitantly allow a control of its stereochemistry. It was anticipated that the fused C−D rings of **IV** could be elaborated through an intramolecular reaction between the dienyl system of **V** and an imine or an iminium electrophile, generated in situ from the ethylamino chain. Activation of the imine could be carried out in several ways as a function of the nature of the R′ substituent. Further elaboration of the 1,3-diene moiety of **IV**, followed by formation of ring-B through a Friedel−Crafts reaction from **III**, should complete the synthesis. Three different approaches have thus been devised to construct skeleton **IV**, varying the nature of the aldehyde and that of the starting amine.

Scheme 1. Disconnection Approach to Isoquinoline Alkaloids



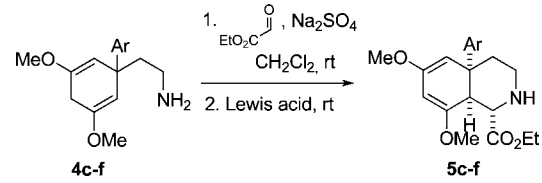
Arylcyclohexadiene precursors are easily available through Birch reductive alkylation of suitably substituted biaryls **VI**,[6] followed by the reduction of the nitrile group into the desired ethylamino chain. A series of arylcyclohexadienes **4a**−**f** were thus prepared, which were then condensed with ethyl glyoxylate to produce in situ the corresponding imine. In a preliminary experiment, an unseparable 74:26 mixture of **4b** and its regioisomer **4a** (issued from the Birch reduction) was submitted to the copper-catalyzed reaction (Scheme 2). **4b** reacted efficiently and exclusively on the enol ether side to give **5b** as a single diastereomer possessing three new stereogenic centers, including the quaternary center present in the targeted alkaloids. In contrast, its isomer **4a** was recovered unchanged, suggesting that these dienes react as enol ethers through a Mannich-type process.[7]

Scheme 2. Copper-Mediated Cyclization of Dienes **4a**,**b**



Similarly, analogues **4c**−**f** provided, under Lewis acid catalysis, using either $CuClO_4(CH_3CN)_4$[8] or $Yb(OTf)_3$,[9] the desired aza-decaline **5c**−**f** in excellent yields (Table 1), as single diastereomers.

Table 1. Lewis-Acid Mediated Cyclizations of Dienes **4c**−**f**



entry	Ar	cat.[a]	diene	product	yield[b]
1	Ph	Cu	**4c**	**5c**	96(73)
2	3-MeO-4-BnOPh	Cu	**4d**	**5d**	79
3	3-MeOPh	Cu	**4e**	**5e**	89
4	3,5-$(MeO)_2$Ph	Yb	**4f**	**5f**	quant.

[a] Cu: $CuClO_4(CH_3CN)_4$; Yb: $Yb(OTf)_3$. [b] Yield estimated from the ^1H NMR of the crude reaction mixture (isolated yields after chromatography).

The imine intermediate may be isolated first, before being submitted to the Lewis acidic conditions. Alternatively, the two steps may be carried out in one pot by successive formation of the imine and addition of the Lewis acid to the crude reaction mixture (Supporting Information). While crude yields were generally high, we noticed that chromatography resulted in a loss of material over silica (entry 1, Table 1). The relative configuration of bicyclic amine **5c** was obtained from X-ray diffraction studies carried out on intermediate **6** (Scheme 3). The latter was obtained, as a crystalline compound, through a regioselective hydrolysis of the bisenol

(5) (a) Abd Rahman, N.; Landais, Y. *Curr. Org. Chem.* **2002**, *6*, 1369–1395. (b) Studer, A.; Schleth, F. *Synlett* **2005**, 3033–3041. (c) Elliott, M. C.; Paine, J. S. *Org. Biomol. Chem.* **2009**, *7*, 3455–3462. (d) Maji, M. S.; Frohlich, R.; Studer, A. *Org. Lett.* **2008**, *10*, 1847–1850. (e) Umeda, R.; Studer, A. *Org. Lett.* **2007**, *9*, 2175–2178. (f) Butters, M.; Elliott, M. C.; Hill-Cousins, J.; Paine, J. S.; Walker, J. K. E. *Org. Lett.* **2007**, *9*, 792–803. (g) Errasti, G.; Koundé, C.; Mirguet, O.; Lecourt, T.; Micouin, L. *Org. Lett.* **2009**, *11*, 2912–2915. (h) Umeda, R.; Studer, A. *Org. Lett.* **2008**, *10*, 993–996. (i) Roberson, C. W.; Woerpel, K. A. *J. Am. Chem. Soc.* **2002**, *124*, 11342–11348. (j) Chappell, D.; Drew, M. G. B.; Gibson, S.; Harwood, L. M.; Russell, A. T. *Synlett* **2010**, 517–520.

(6) (a) Lebeuf, R.; Dunet, J.; Beniazza, R.; Ibrahim, D.; Bose, G.; Robert, F.; Landais, Y. *J. Org. Chem.* **2009**, *74*, 6469–6478. (b) Lebeuf, R.; Robert, F.; Landais, Y. *Org. Lett.* **2005**, *7*, 4557–4560.

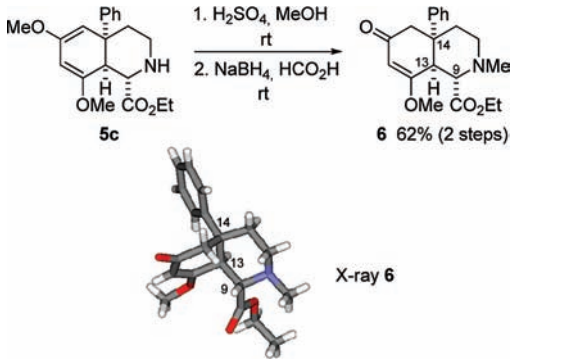
(7) An imino-ene-type process may also be envisioned.

(8) Yao, S.; Fang, X.; Jorgensen, K. A. *Chem. Commun.* **1998**, 2547–2548.

(9) (a) Jia, Q.; Xie, W.; Zhang, W.; Janczuk, A.; Luo, S.; Zhang, B.; Cheng, J. P.; Ksebati, M. B.; Wang, P. G. *Tetrahedron Lett.* **2002**, *43*, 2339–2342. (b) Tietze, L. F.; Utecht, J. *Chem. Ber.* **1992**, *125*, 2259–2263.

ether moiety of **5c** with H_2SO_4, followed by methylation, using $NaBH_4-HCO_2H$.[10] X-ray crystallography of **6** led us to assume that **5b**−**f** all possess the same C9−C13−C14 *trans*−*cis* relative configuration.[11]

Scheme 3. Synthesis and X-ray Structure of **6**



The high stereoselectivity observed above could be rationalized invoking an *exo*-transition state with a metal-complexed (*E*)-imino ester (Figure 2). The chairlike conformation in the *exo* approach appears more favorable than the boatlike conformation of the *endo* mode.

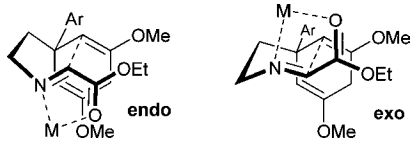
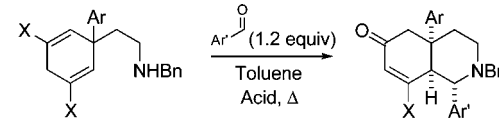


Figure 2. Transition state model for the metal-catalyzed cyclization of imines issued from dienes **4**.

Encouraged by these results, we devised a second route with the aim of directly generating protected secondary amines, starting from more reactive iminium salts.[12] For this purpose, benzyl amines **7a**−**c**[13] were reacted with aromatic aldehydes in the presence of an equimolar amount of Brönsted (Table 2) or Lewis acids. Benzaldehyde and furfural were found to be the most suitable candidates, while ethyl glyoxylate was discarded, giving rise to a complex mixture of products under the reaction conditions. As before, "naked" 1,4-arylcyclohexadiene **7a** led to no reaction (entry 1, Table 2), whatever the conditions tested, indicating that these olefins were not nucleophilic enough to react with iminium species. After extensive studies, precursor **7b** led upon reaction with 1.2 equiv of benzaldehyde in the presence of benzoic acid (1 equiv) to a moderate yield of bicyclic benzylamine **8b** (entry 2). It is noteworthy that the cyclization was accompanied by the regioselective hydrolysis of one of the enol ethers. Among other acids tested, Lewis acidic BF_3-OEt_2 and $B(OH)_3$[12] gave only recovered starting material, whereas pyridinium *p*-toluene sulfonate (PPTS, entry 3) led to moderate yield of **8b**. Using trifluoroacetic acid (entry 4) or decreasing the temperature from 115 to 70 °C (entry 5) led to similar results. In constrast, furfural was found to be more reactive under the given conditions, offering access to the desired amines **8c**,**d** in excellent yields as a single diastereomer in each case (entries 7 and 8).[14]

Table 2. Acid-Mediated Cyclizations of Dienes **7a**−**c**



7a, X = H; Ar = Ph
7b, X = OMe; Ar = Ph
7c, X = OMe; Ar = 3-MeOPh
8a-d

entry	diene	Ar'	acid[a]	*t* (h)	product[e]	yield[f]
1	**7a**	Ph	$PhCO_2H$	20[c]	**8a**	-
2	**7b**	Ph	$PhCO_2H$	21[c]	**8b**	50
3	**7b**	Ph	PPTS	21[c]	**8b**	37
4	**7b**	Ph	TFA	21[c]	**8b**	50
5	**7b**	Ph	TFA	21[d]	**8b**	52
6	**7b**	Ph	TFA[b]	21[d]	**8b**	47
7	**7b**	furyl	TFA	21[d]	**8c**	96[g]
8	**7c**	furyl	TFA	21[d]	**8d**	83[g]

[a] 1 equiv of acid was used. [b] 0.5 equiv of TFA was used. [c] 115 °C. [d] 70 °C. [e] dr > 98:2 as measured from ^1H NMR of the crude reaction mixture. [f] Isolated yield of **8a**−**d** after chromatography. [g] Crude yields. Used without purification.

The relative configuration of tertiary amines **8b**−**d** was assigned based on the X-ray structure determination of ketoacetamide **9** (Figure 3), obtained from **8d**,[15] and was found identical to that obtained using the first approach. Importantly, examination of the crystal structure of **9** revealed that aromatic substituents at C9 and C14 are in close proximity, as a result of $A_{1,3}$-strain,[16] induced by the acetamide group. This point is critical for the future functionalization of these substrates, which includes in the late stage a Friedel−Crafts reaction between the phenyl ring (C14) and a carbonyl group at C9,[17] which will be generated through the oxidation of the furyl ring.[18] The short distance between both aromatic groups, estimated to be in the range of 3.4 to 3.6 Å, indicates that such a close proximity should allow the coupling between these entities and construction of ring B.

(10) Gribble, G. W.; Lord, P. D.; Skotnicki, J.; Dietz, S. E.; Eaton, J. T.; Johnson, J. L. *J. Am. Chem. Soc.* **1974**, *96*, 7812–7814.
(11) Numbering follows that of the natural products **1**−**3** (Figure 1).
(12) (a) Parsons, R. L.; Berk, J. D.; Kuehne, M. E. *J. Org. Chem.* **1993**, *58*, 7482–7489. (b) Kuehne, M. E.; Xu, F. *J. Org. Chem.* **1997**, *62*, 7950–7960.
(13) Benzylamines were easily formed through reductive amination of amine **4c**,**d** with benzaldehyde (Supporting Information).
(14) No trace of the other diastereomer could be detected from the ^1H NMR of the crude reaction mixture.
(15) **8d** was converted in 5 steps into ketone **9** (Supporting Information). It is assumed that no epimerization took place under the reaction conditions.
(16) Hoffmann, R. W. *Chem. Rev.* **1989**, *89*, 1841–1860.
(17) Kano, S.; Yokomatsu, T.; Nemoto, H.; Shibuya, S. *J. Am. Chem. Soc.* **1986**, *108*, 6746–6748.

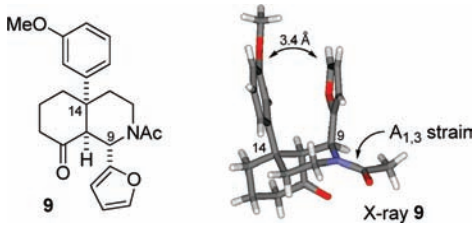
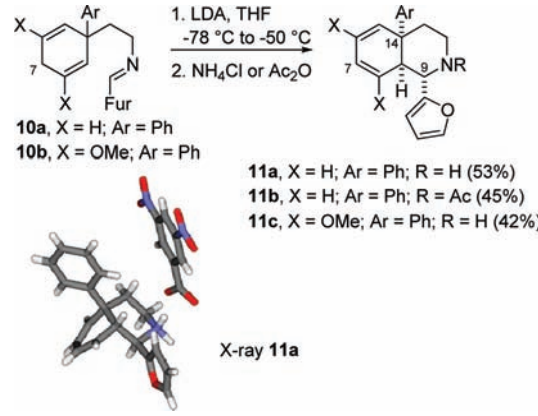


Figure 3. X-ray structure determination of octahydroisoquinolines **9**.

The results above have shown that electron-rich dienyl systems are more reactive, which strongly supports a Mannich-type mechanism for the copper- and acid-mediated cyclization of enol ethers **4b**−**f** and **7b**−**c**. In contrast, 1,4-dienes lacking OMe substituents (i.e., **7a**) do not react under these conditions. We therefore envisaged a complementary approach that would offer access to a C ring at a lower oxidation state that could be easily functionalized later, to access isoquinoline alkaloids. This third approach is based on an anionic-mediated cyclization using lithium amides. It was foreseen that the acidic bis-allylic proton at C7 (pK_a∼35 in DMSO)[4b] of dienes **4** and **7** would be abstracted under such basic conditions[4b,5i,19] to provide a pentadienyl anion that could then cyclize by reaction with the imine functional group. Imine **10a** was thus prepared by condensing the corresponding amine with furfural, then treated with LDA (1.1 equiv), furnishing, after acidic workup, the desired bicyclic amine **11a** as a unique diastereomer, albeit in moderate yield (Scheme 4). Similarly, workup using acetic anhydride led to acetamide **11b**, again as a single diastereomer. Interestingly, the methodology could also be applied to diene **10b** having enol ether groups.

Cyclization of **10b** thus provided octahydroisoquinoline **11c** in moderate yield. The relative configuration of **11a**−**c** was determined through X-ray diffraction studies on a 2,4-dinitrobenzoic acid salt of **11a** and proved to be the same as that observed before for the first two approaches. This strategy thus offers a one-pot approach to octahydroisoquinoline having a "naked" cyclohexa-1,3-diene moiety, ready for further functionalization, and an *N*-acetyl-protected amine that should, as in **9**, force substituents at C9 and C14 to be in close proximity through the $A_{1,3}$-strain.

Scheme 4. LDA-Mediated Cyclizations of Dienes **10a**,**b**



In summary, we have described along these lines a new and straightforward access to an A−C−D tricyclic skeleton of morphinans from symmetrical arylcyclohexadienes. Three complementary approaches have been devised, which provide the octahydroisoquinoline moiety with the relative configuration of pallidinine and congeners in no more than three or four steps from simple biaryls. This strategy also provides a simple solution to the critical problem of the control of the stereochemistry of the quaternary center in the synthesis of isoquinoline alkaloids.[1b] Studies are now underway in our laboratory to functionalize intermediates such as **5**, **8**, and **11** en route to pallidinine synthesis.

Acknowledgment. We thank the MNERT and CNRS for financial support and grants for JD, RL, and GB. We are grateful to B. Kauffmann (IECB, Bordeaux) for X-ray diffraction studies and J. C. Lartigues and N. Pinaud (ISM, University Bordeaux-1) for NMR experiments.

Supporting Information Available: Experimental details and spectral data for new compounds and cif files for **6**, **9**, and **11a**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL1004627

(18) Danishefsky, S. J.; DeNinno, M. P.; Chen, S.-H. *J. Am. Chem. Soc.* **1988**, *110*, 3929–3940.
(19) Studer, A.; Amrein, S. *Angew. Chem., Int. Ed.* **2000**, *39*, 3080–3082.