Organic LETTERS

Letter

pubs.acs.org/OrgLett

Synthesis of the Tetracyclic ABCD Ring Systems of Madangamines D−F

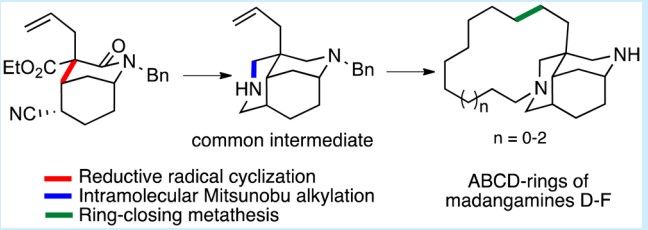
Faïza Diaba,*[,†] Climent Pujol-Grau,[†] Agustín Martínez-Laporta,[†] Israel Fernández,[‡] and Josep Bonjoch*[,†]

[†]Laboratori de Química Orgànica, Facultat de Farmàcia, IBUB, Universitat de Barcelona, Av. Joan XXIII s/n, 08028 Barcelona, Spain

[‡]Departamento de Química Orgánica I, Facultad de Ciencias Químicas, Universidad Complutense de Madrid, 28040 Madrid, Spain

Supporting Information

ABSTRACT: Synthesis of the tetracyclic cores of madangamines D−F was achieved, featuring a reductive radical process from an ethoxycarbonyldichloroacetamide to build the morphan nucleus, a Mitsunobu-type aminocyclization toward the common diazatricyclic intermediate, and ring-closing metathesis reactions for the macrocyclization step leading to the 13- to 15-membered rings.



Madangamines are a group of 3-alkylpiperidine marine alkaloids embodying a pentacyclic skeleton.[1] The six madangamines isolated so far have in common a perhydro-6,4-(iminomethano)isoquinoline core (ABC ring)[2−4] and a western macrocycle of 13 to 15 members. Madangamines A−E contain an eastern polyunsaturated ring and madangamine F shows a greater oxidation state in rings B and E (Figure 1). Their

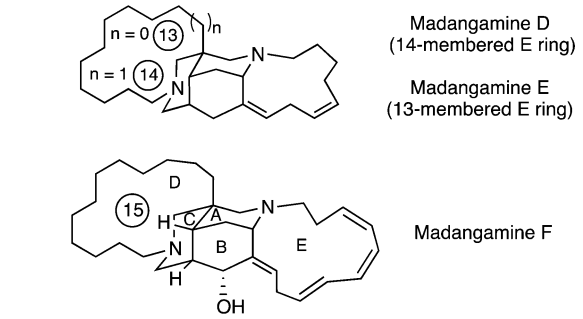
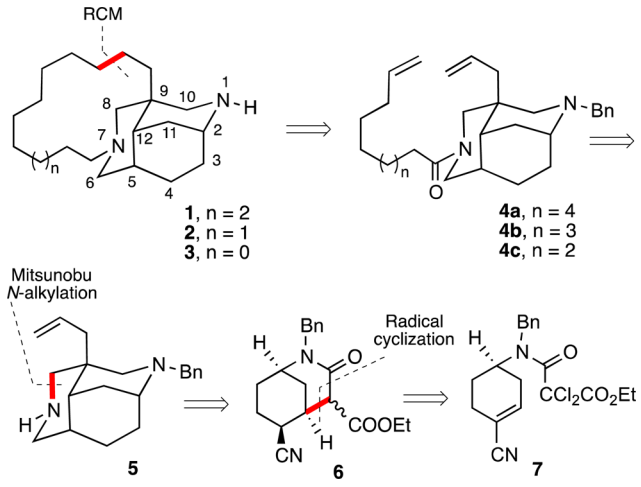


Figure 1. Madangamines D−F embodying a macrocyclic saturated D-membered ring.

biological activities, coupled with a highly complex structure, have made these alkaloids attractive synthetic targets. However, only one member of this family, madangamine D, has been achieved by total synthesis, in recent work by Amat and Bosch.[5] Four other approaches have been developed to access the madangamine ABC diazatricyclic core using either hydroisoquinolines[6] or 2-azabicyclo[3.3.1]nonanes (morphans) as intermediate platforms.[7,8]

Herein, we report a synthetic approach to the tetracyclic cores of madangamines D−F from a common precursor. As depicted in Scheme 1, the synthetic strategy we pursued toward our goal, macrocycles **1**−**3**, leads back, via the dienes **4**, to diazatricyclic compound **5**, which served as a strategic point of divergence en route to these targeted compounds. Overall, ring-closing

Scheme 1. Retrosynthetic Strategy for Synthesis of the Tetracyclic ABCD Rings of Madangamines



metathesis (RCM)[9] macrocyclizations of dienes **4** were required in the range of 13- to 15-membered rings. The polyfunctionalized morphan[10] **6** was envisaged as an early stage intermediate from which an allyl group would be selectively introduced at C9. The nitrile at C5 and the ester at C9 stemming from the morphan cyclization would undergo reduction for the synthesis of a useful amino alcohol to promote the ring closure leading to **5**. Morphan **6** would be accessed by the reductive radical cyclization of alkoxycarbonyldichloroacetamide **7**, thereby expanding the scope of haloacetamides able to generate radical species for the building of nitrogen-containing rings, either in reductive[11] or atom-transfer radical cyclizations.[12] The usefulness of radical synthetic methods for constructing valuable intermediates in

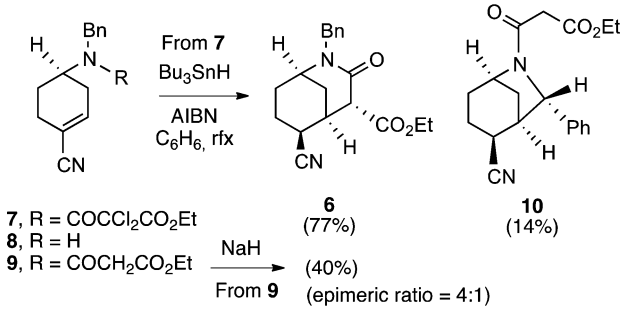
Received: December 12, 2014

DOI: 10.1021/ol503586d
Org. Lett. XXXX, XXX, XXX−XXX

target-oriented natural product synthesis would thus be enhanced.[13,14]

The synthesis began with the 4-(benzylamino)cyclohex-1-encarbonitrile (**8**), which was available in six steps from the monoethylene acetal of 1,4-cyclohexanedione using a protocol without any chromatographic purification.[15] This secondary amine was acylated with 2,2-dichloro-2-ethoxycarbonylacetyl chloride,[16] and the resulting dichloroamido ester **7** was treated with Bu_3SnH to induce a reductive radical cyclization[17] leading to the bridged morphan nucleus **6** in 77% yield (Scheme 2).

Scheme 2. Radical vs Ionic Cyclization toward the Morphan Ring



Notably, attempts to obtain **6** by an ionic intramolecular Michael reaction from amido ester **9**, also available from **8**, gave poor results, not only because of the overall yield but also, and even more importantly, due to the low stereocontrol. The lack of diastereoselectivity (**6** was isolated as a 4:1 epimeric mixture at C5, using NaH as the base) seems inherent to the process, since it is known that the equatorial protonation of exocyclic α-cyano cyclohexyl anions can occur, leaving an axial cyano substituent.[18]

Some interesting results were observed in the radical cyclization: (i) the formation of **6** was diastereoselective, the stereochemistry at C5 and C9 in morphan **6** being well-defined, since the cyano group at C5 was equatorially located by a kinetic axial delivering of the hydrogen from theBu_3SnH and the ester group at C9 has an axial disposition (Figure 2), and (ii) a

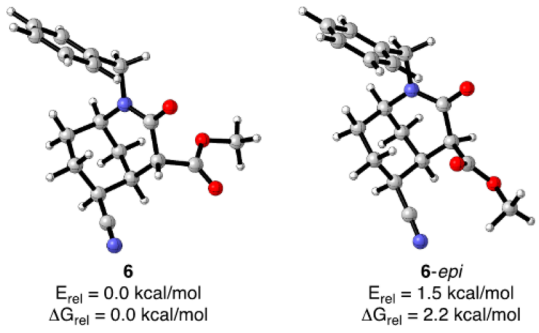


Figure 2. Fully optimized geometries (B3LYP/6-31+G(d) level) and relative energies of morphans **6** and **6**-*epi* (methyl esters).

normorphan compound **10** was also isolated as a minor byproduct.[19] The α-amidoyl radical derived from **7** presents two reactive conformations, namely the *Z* rotamer **INT3** and *E* rotamer **INT1**, the latter being required for the cyclization step (Figure 3). Although **INT3** is 5.6 kcal/mol more stable than **INT1**, **6** was formed from rotamer **INT1** via transition state **TS1** ($\Delta G^{\ddagger}$ = 10.9 kcal/mol, from **INT3**). In contrast, normorphan **10** arose from the most stable radical rotamer **INT3**, unable to

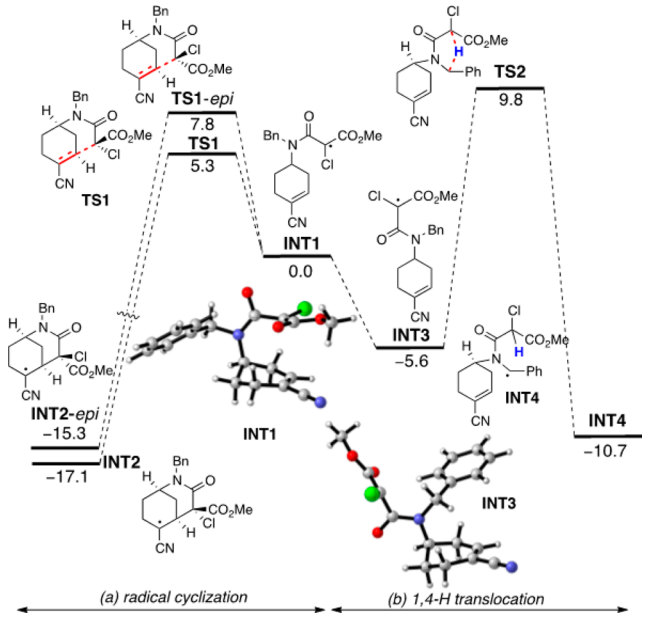


Figure 3. Computed reaction profile (uB3LYP/6-31+G(d) level) for the radical processes from amide rotamers: (a) radical cyclization via **TS1**; (b) 1,4-hydrogen translocation via **TS2**. Relative free energies (ΔG_{298}, at 298 K) are given in kcal/mol.

undergo radical cyclization, which underwent a 1,4-H radical translocation[20] in a more energetically demanding process ($\Delta G^{\ddagger}$ = 15.4 kcal/mol, via **TS2**) followed by a radical cyclization to the normorphan nucleus (a complete profile of the process based on density functional theory calculations is included in the Supporting Information). Therefore, it can be concluded that the favored formation of the morphan-cyclized compound takes place mainly under kinetic control.[21]

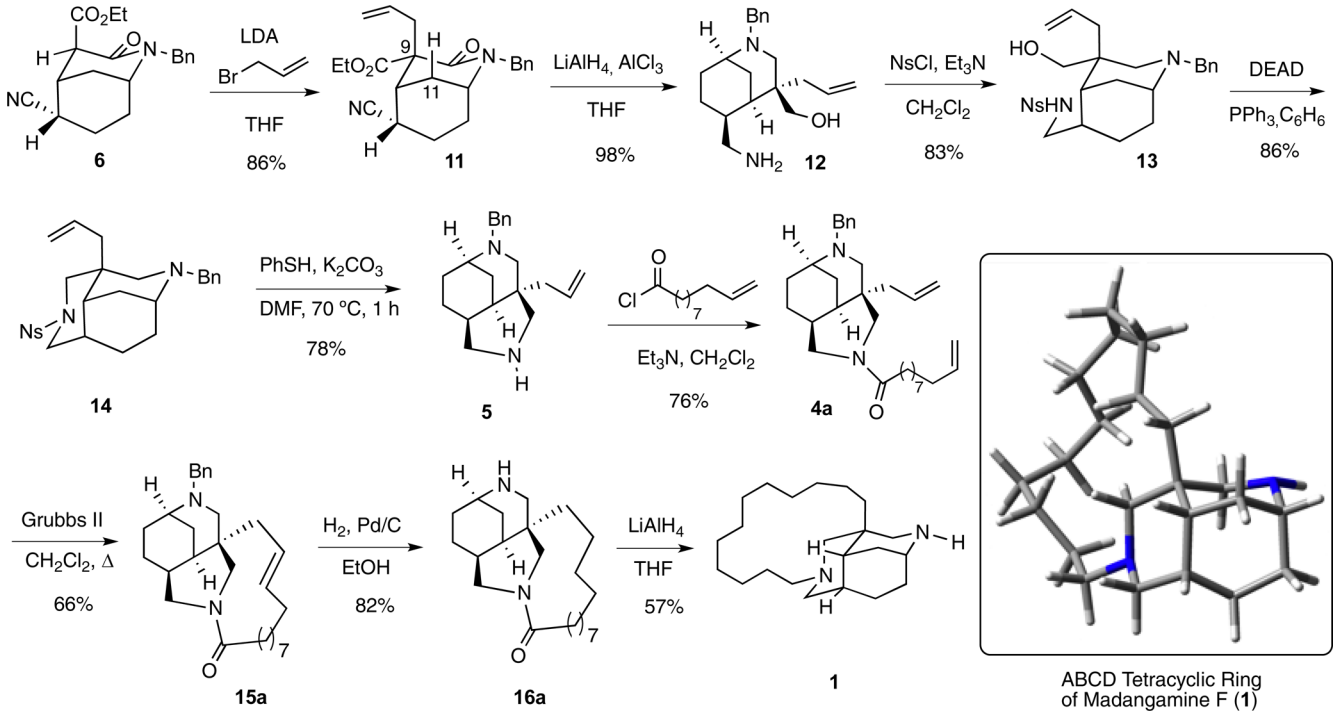
The next step from morphan **6**, involving the generation of the quaternary stereogenic center, was the chemoselective allylation upon the methine at C9, which took place from the top face under a sterically controlled kinetic reaction to give exclusively **11**[22] (Scheme 3). The configuration in the stereogenic quaternary center in **11** was established unequivocally from a NOESY NMR spectrum in which a methylene proton of the side chain at δ 2.65 give a cross-peak with the H-11 (*pro-S*) at δ 2.20. In the following step, the reduction of the carbonyl lactam, nitrile, and ester groups was carried out in only one operation by treatment of **11** with alane, generated in situ from $LiAlH_4$ and $AlCl_3$. The process gave the diamino alcohol **12** in high yield. For the ring closure of the piperidine A ring, a Fukuyama protocol was used involving an initial nosylation and further intramolecular alkylation through a Mitsunobu process. Removal of the nosyl group rendered the secondary amine **5**, which constitutes the common advanced synthetic intermediate en route to the three diazatetracyclic targets.

Amide bond formation between secondary amine **5** and 10-undecenoic acid chloride afforded the RCM precursor **4a** in 83% yield. The RCM of **4a** was undertaken using Grubbs second-generation catalyst in CH_2Cl_2 (3.3 mM) to give the cyclized product **15a** in 66% yield. Finally, adjustment of the oxidation level by hydrogenation with a concomitant *N*-debenzylation gave **16a**, which by reduction with $LiAlH_4$ finally rendered the target **1**. The overall yield for the synthesis of the tetracyclic ring of madangamine F, **1**, was 6.2% over 17 steps.

Having achieved the first target, we pursued synthetic access to the 14- and 13-macrocyclic ring analogues following the same

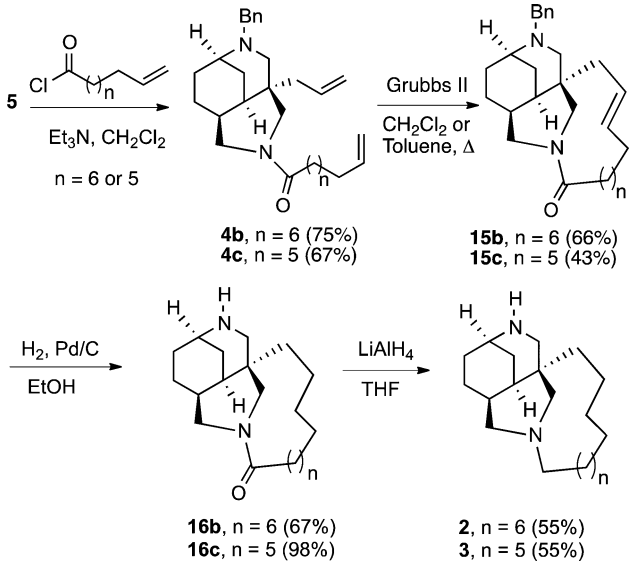
DOI: 10.1021/ol503586d
Org. Lett. XXXX, XXX, XXX−XXX

Scheme 3. Synthesis of the Tetracyclic Core of Madangamine F



protocol, i.e., using the secondary amine **5** as a common intermediate. Thus, treatment of **5** with 9-decenoic and 8-nonenoic acid chlorides led to the amides **4b** and **4c**, respectively, in good yields. RCM from **4b** took place under the same reaction conditions as used from **4a** (Scheme 4). As expected, the

Scheme 4. Synthesis of Tetracyclic ABCD Rings of Madangamines D and E



formation of the 13-membered ring was more difficult as a consequence of the higher strain imposed by the double bond in this particular macrocycle.[23] Indeed, the cyclization did not proceed when **4c** in CH_2Cl_2 was used as a solvent, but when toluene at 80 °C was used with 1,4-benzoquinone as an additive,[24] macrocycle **15c** was isolated in 43% yield. Hydrogenation of **15b** and **15c** allowed us to isolate the tetracyclic compounds **16b** and **16c**, respectively, which after reduction of the lactam moiety rendered **2** (37% over two steps) and **3** (53% over two steps).

In summary, a 17-step approach for the construction of the ABCD ring system of madangamines F, E, and D was successfully developed. We have shown that radical chemistry is a powerful tool for the stereoselective synthesis of the highly functionalized AB ring system. The synthetic pathway gave access to the three different ABCD fragments of madangamines from a common intermediate. This chemistry will pave the way for the total synthesis of madangamines.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, spectroscopic and analytical data, and copies of NMR spectra of new compounds. The computed complete profile of the radical process leading to **6** and **10** and Cartesian coordinates and energies for all the species considered. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: faiza.diaba@ub.edu.
*E-mail: josep.bonjoch@ub.edu.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Support of this research was provided by the Spanish MINECO and FEDER (Project Nos. CTQ2013-41338-P and CTQ2013-44303-P).

DOI: 10.1021/ol503586d
Org. Lett. XXXX, XXX, XXX−XXX

REFERENCES

(1) (a) Andersen, R. J.; van Soest, R. W. M.; Kong, F. *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Pergamon-Elsevier: Oxford, 1996; Vol. *10*, pp 301−355. (b) Berlinck, R. G. S. Polycyclic Diamine Alkaloids from Marine Sponges. *Topics in Heterocyclic Chemistry*; Springer: Berlin, 2007; vol. *10*, pp 211−238.

(2) Madandamine, A.; Kong, F.; Andersen, R. J.; Allen, T. M. *J. Am. Chem. Soc.* **1994**, *116*, 6007−6008.

(3) Madangamines, B.-E.; Kong, F.; Graziani, E. I.; Andersen, R. J. *J. Nat. Prod.* **1998**, *61*, 267−271.

(4) Madangamine, F.; Oliveira, J. H. H. L.; Nascimento, A. M.; Kossuga, M. H.; Cavalcanti, B. C.; Pessoa, C. O.; Moraes, M. O.; Macedo, M. L.; Ferreira, A. G.; Hajdu, E.; Pinheiro, U. S.; Berlinck, R. G. S. *J. Nat. Prod.* **2007**, *70*, 538−543.

(5) (a) Ballette, R.; Pérez, M.; Proto, S.; Amat, M.; Bosch, J. *Angew. Chem., Int. Ed.* **2014**, *53*, 6202−6205. (b) For a preliminary ABCD ring approach, see: Amat, M.; Ballette, R.; Proto, S.; Pérez, M.; Bosch, J. *Chem. Commun.* **2013**, *49*, 3149−3151.

(6) For approaches to the ABC tricyclic fragment of madangamines from hydroisoquinolines (BC rings), see: (a) Matzanke, N.; Gregg, R. J.; Weinreb, S. M.; Parvez, M. *J. Org. Chem.* **1997**, *62*, 1920−1921. (b) Quirante, J.; Paloma, L.; Diaba, F.; Vila, X.; Bonjoch, J. *J. Org. Chem.* **2008**, *73*, 768−771. (c) Amat, M.; Pérez, M.; Proto, S.; Gatti, T.; Bosch, J. *Chem.—Eur. J.* **2010**, *16*, 9438−9441.

(7) For approaches from 2-azabicyclo[3.3.1]nonanes (AB rings), see: (a) Yamazaki, N.; Kusanagi, T.; Kibayashi, C. *Tetrahedron Lett.* **2004**, *45*, 6509−6512. (b) Tong, H. M.; Martin, M.-T.; Chiaroni, A.; Bénéchie, M.; Marazano, C. *Org. Lett.* **2005**, *7*, 2437−2440.

(8) For the synthesis of the ACE rings, see: (a) Yoshimura, Y.; Inoue, J.; Yamazaki, N.; Aoyagi, S.; Kibayashi, C. *Tetrahedron Lett.* **2006**, *47*, 3489−3492. (b) Proto, S.; Amat, M.; Pérez, M.; Ballette, R.; Romagnoli, F.; Mancinelli, A.; Bosch, J. *Org. Lett.* **2012**, *14*, 3916−3919. A preliminary work on madangamine alkaloids field has been presented: (c) Dixon, D. J. Abstracts of Papers, *244th ACS National Meeting*, Philadelphia, 2012; American Chemical Society: Washington, DC, 2012; ORG-105.

(9) (a) Gradillas, A.; Pérez-Castells, J. *Angew. Chem., Int. Ed.* **2006**, *45*, 6086−6101. (b) Wang, C.; Yu, M.; Hoveyda, A. H.; Kyle, A. F.; Jakubec, P.; Dixon, D. J.; Schrock, R. R. *Chem.—Eur. J.* **2013**, *19*, 2726−2740 and references cited therein.

(10) For a review of 2-azabicyclo[3.3.1]nonanes and their application to natural product synthesis, see: Bonjoch, J.; Diaba, F.; Bradshaw, B. *Synthesis* **2011**, 993−1018.

(11) (a) Quirante, J.; Escolano, C.; Merino, A.; Bonjoch, J. *J. Org. Chem.* **1998**, *63*, 968−976. (b) Cassayre, J.; Quiclet-Sire, B.; Saunier, J.-B.; Zard, S. Z. *Tetrahedron Lett.* **1998**, *39*, 8995−8998. (c) Cassayre, J.; Zard, S. Z. *Synlett* **1999**, 501−503.

(12) (a) Hirai, Y.; Hagiwara, A.; Terada, T.; Yamazaki, T. *Chem. Lett.* **1987**, 2417−2418. (b) Seijas, J. A.; Vázquez-Tato, M. P.; Castedo, L.; Estévez, R. J.; Onega, M. G.; Ruiz, M. *Tetrahedron* **1992**, *48*, 1637−1642. (c) Li, Q.; Li, G.; Ma, S.; Feng, P.; Shi, Y. *Org. Lett.* **2013**, *15*, 2601−2603. (d) Diaba, F.; Martínez-Laporta, A.; Bonjoch, J. *J. Org. Chem.* **2014**, *79*, 9365−9372.

(13) For a classical review, see: Jasperse, C. P.; Curran, D. P.; Flevig, T. L. *Chem. Rev.* **1991**, *91*, 1237−1286.

(14) (a) Quiclet-Sire, B.; Zard, S. Z. *Beilstein J. Org. Chem.* **2013**, *9*, 557−576. (b) Bonjoch, J.; Bradshaw, B.; Diaba, F. In *Stereoselective Synthesis of Drugs and Natural Products*; Andrushko, V., Andrushko, N., Eds.; Wiley-VCH: New York, 2013; pp 733−768.

(15) Compound **8** was prepared in a six-step sequence on a 3-g scale without any intermediate purification step (86% overall yield).

(16) Castelfranchi, G.; Perrotti, E. *Ann. Chim. (Rome)* **1957**, *47*, 1201−1224.

(17) Treatment of dichloro ester **7** under atom-transfer radical cyclization conditions gave a mixture of compounds: Diaba, F.; Martínez-Laporta, A.; Bonjoch, J. *Eur. J. Org. Chem.* **2014**, 2371−2378.

(18) For protonation of cyclohexyl anions, see: Lüning, U.; Baumgartner, H.; Manthey, C.; Meynhardt, B. *J. Org. Chem.* **1996**, *61*, 7922−7926. See also: Klein, J. *Tetrahedron* **1974**, *30*, 3349−3353. Hoz, S.; Azran, C.; Sella, A. *J. Am. Chem. Soc.* **1996**, *118*, 5456−5461.

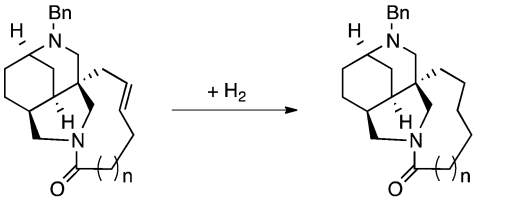
(19) The reductive cyclization of the analogous trichloroacetamide of **7** (Cl atom instead of CO_2Et) exclusively gave the cyclized morphan in 84% yield, with no traces of a normorphan compound being detected.

(20) For a review of 1,*n*-hydrogen atom transfer reactions, see: Nechab, M.; Mondal, S.; Bertrand, M. P. *Chem.—Eur. J.* **2014**, *20*, 16034−16059.

(21) The product distribution (**6**/**10**) is controlled by the difference between the total free energy of activation for each pathway (Curtin−Hammett principle) and is not dictated by the rotamer ratio in the starting material **7** (*Z*/*E* = 1:4, see ref 17).

(22) Using a reverse addition, a minor amount of the epimer at C9 was also isolated (see the Supporting Information).

(23) As an estimation of the ring strain, we have computed the hydrogenation heats of macrocycles **15**. As shown below, the hydrogenation of **15c** is the most exothermic process, which correlates with the higher ring strain imposed by the double bond in the thirteen-membered ring (energy values are given in kcal/mol).



15a, n = 7
15b, n = 6
15c, n = 5

ΔE (ΔG)
16a, n = 7, −20.2 (−13.2)
16b, n = 6, −22.1 (−15.6)
16c, n = 5, −23.5 (−16.3)

(24) 1,4-Benzoquinone acts as scavenger of ruthenium hydride species that might be formed during the reaction and cause decomposition: (a) Hong, S. H.; Sanders, D. P.; Lee, C. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2005**, *127*, 17160−17161. (b) Toya, H.; Satoh, T.; Okano, K.; Takasu, K.; Ihara, M.; Takahashi, A.; Tanaka, H.; Tokuyama, H. *Tetrahedron* **2014**, *70*, 8129−8141.

DOI: 10.1021/ol503586d
Org. Lett. XXXX, XXX, XXX−XXX