Tetrahedron Letters 52 (2011) 6899–6902

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

A practical *one-pot* radical-ionic sequence for the preparation of epoxides: application to the synthesis of unnatural polyhydroxylated alkaloids

Eduardo Peralta-Hernández, Omar Cortezano-Arellano, Alejandro Cordero-Vargas *

Instituto de Química, Universidad Nacional Autónoma de México, Circuito Exterior s/n, Ciudad Universitaria, 04510 México D.F., Mexico

ARTICLE INFO

Article history:
Received 20 September 2011
Revised 5 October 2011
Accepted 7 October 2011
Available online 15 October 2011

Keywords:
Free radical
Atom transfer reaction
Epoxides
Polyhydroxylated alkaloids

ABSTRACT

An efficient *one-pot* sequence for the preparation of epoxides from α-iodoesters or α-iodonitriles and allylic alcohols is described. This sequence is based on the use of iodine atom transfer reaction onto allylic alcohols followed by a ring closing epoxidation reaction of the halohydrin intermediates. The feasibility of this sequence is showcased in the synthesis of the perhydroaza-azulene, an unnatural analog of castanospermine.

Introduction

Since their isolation, polyhydroxylated indolizidine alkaloids like (+)-castanospermine (**1**),[1] (−)-swainsonine (**2**),[2] and (+)-lentiginosine (**3**)[3] have attracted the attention of synthetic organic chemists due to their interesting structures and promising pharmaceutical applications.[4] In recent years, much effort has been made in order to synthesize stereochemically different and ring expanded analogs of the above-mentioned aza-sugars because in some cases, these analogs have shown increased glycosidase inhibitory and immunosuppressive activities.[5] In this regard, Dhavale and co-workers have successfully synthesized tetrahydroxylated perhydroaza-azulenes **4a** and **4b**[6] as well as a single seven-membered ring analog **5**[5b] (Fig. 1).

An efficient strategy for the preparation of pyrrolidines is through a 5-*exo-tet* cyclization of a primary or secondary amine onto an epoxide, which leads to the desired five-membered cyclic amine bearing a hydroxyl group with known stereochemistry.[6] In this Letter, we report an accessible *one-pot* sequence for the straightforward preparation of epoxides from either α-iodoesters or α-iodonitriles and allylic alcohols based on a free-radical atom-transfer reaction followed by a base-promoted cyclization. This sequence was applied to the synthesis of tetrahydroxylated perhydroaza-azulene **4a**.

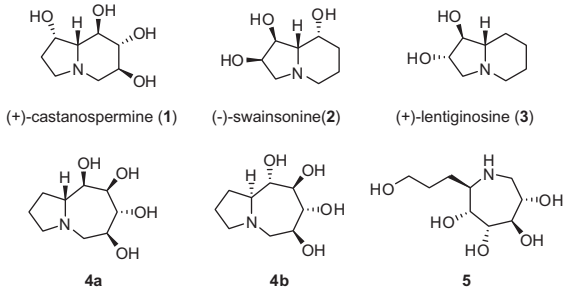
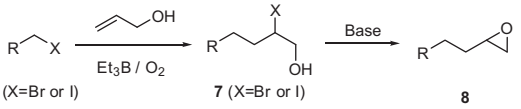


Figure 1. Natural and synthetic polyhydroxylated alkaloids.



Scheme 1. Radical-ionic strategy for the preparation of epoxides.

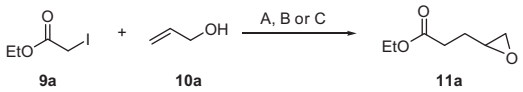
Results and discussion

Our strategy for the direct preparation of epoxides is depicted in scheme 1. We reasoned that a Kharash-type reaction[7] between an alkyl halide (**6**), serving as the radical precursor, and an allyl alcohol would afford adduct **7**, which upon treatment with a base, would furnish the desired epoxide **8**. The use of radical conditions for the first step, which are neutral and compatible with other

* Corresponding author. Tel.: +52 55 56224450; fax: +52 55 56162217.
E-mail address: acordero@unam.mx (A. Cordero-Vargas).

0040-4039/$ - see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2011.10.042

Table 1
Optimization of reaction conditions



9a **10a** **11a**

Conditions[a]	Initiator	Solvent(s)	Base	Yield (%)
A	Et_3B	$EtOH/H_2O$	K_2CO_3	49
B	Et_3B	CH_2Cl_2	DBU	78
C	Et_3B	(i)$EtOH/H_2O$ (ii) CH_2Cl_2	DBU	80

[a] Conditions A: Et_3B (1.0 M solution in THF), O_2 (trace), K_2CO_3 (2 equiv) in $EtOH/H_2O$ at rt. Conditions B: Et_3B (1.0 M solution in hexanes), O_2 (trace), CH_2Cl_2; then DBU (2 equiv). Conditions C: (i) Et_3B (1.0 M solution in THF), O_2 (trace), $EtOH/H_2O$ at rt. (ii) DBU, CH_2Cl_2.

reagents, would allow the use of an unprotected allylic alcohol and the second step—ionic cyclization—to be done in a *one-pot* manner.

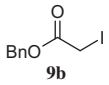
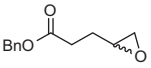
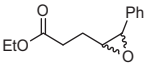
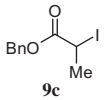
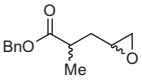
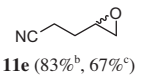
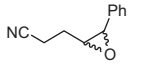
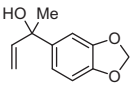
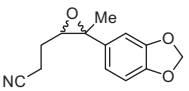
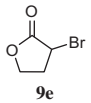
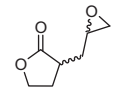
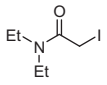
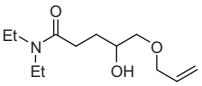
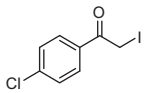
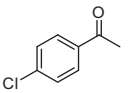
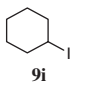
Table 1 shows the optimization of reaction conditions for this transformation. We initially chose ethyl iodoacetate and allyl alcohol as model substrates. In the first attempt (conditions A), both the radical initiator and the base were added since the beginning of the reaction in an aqueous medium, leading to the isolation of the desired product (**11a**), albeit in low yield (49%). Furthermore, using dichloromethane as the solvent and DBU as the base (when the radical reaction was completed), enhanced the yield to 80% (conditions B). Finally, aqueous conditions for the radical step were used again, but adding DBU as the base after switching the solvent to CH_2Cl_2, affording epoxide **11a** in 78% yield (conditions C).

Next, the scope of the procedure was studied for other substrates (Table 2). Good yields were observed for primary stabilized electrophilic radicals such as α-iodoesters **9a**–**b** (entries 1–3) and α-iodonitriles (**9d**, entries 5–7). In the case of substituted allylic alcohols (**10b** and **10c**), nearly equimolar mixtures of *cis*:*trans* isomers were observed in lower yields (entries 3, 6, and 7). The sequence also worked with a secondary electrophilic radical (**9c**, entry 4) and for a bromolactone (**9e**, entry 8), albeit in modest yields (30%). It is worth noting that for the latter substrate, the radical step only succeeded in ethanol–H_2O, which is in agreement with that reported by Fujimoto and co-workers, who proposed that bromine atom transfer is better achieved in solvents with a high dielectric constant.[8] When *N*,*N*′-diethyliodoacetamide **9f** was employed as a radical precursor (entry 9), the expected epoxide was surprisingly not observed, but compound **11j**, which is presumably formed by opening of the initially formed epoxide by allyl alcohol. For α-iodoacetophenone **9g** (entry 10), only the reduced product **11j** was observed, probably due to the formation of the boron enolate prior to the radical addition.[9] On the other hand, nucleophilic radicals **9h** and **9i** failed to carry on the radical reaction (entries 11 and 12), which was somehow expected due to unfavorable polar effects.[10]

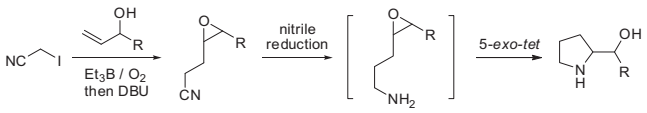
The success of this sequential reaction when α-iodonitriles were used encouraged us to prepare 2-hydroxypirrolidines via a 5-*exo*-*tet* cyclization of 1-amino-5,6-epoxide. Typically, the route for obtaining the mentioned epoxides involves a Claisen–Johnson rearrangement of an allylic alcohol, followed by epoxidation, ester reduction, transformation of the resulting alcohol into a leaving group, substitution by the azide, and reduction of the latter to produce the primary amine which carries on the desired 5-*exo*-*tet* cyclization.[6] By using our protocol, the cyclization precursor would be obtained in only 2 steps (*one pot*) from the corresponding allylic alcohol (Scheme 2).

Based on the above-mentioned strategy for the preparation of 2-hydroxypyrrolidines we proceeded to apply it to the synthesis of perhydroaza-azulenes **4a** and **4b**. As shown in scheme 3, the original route described by Dhavale and co-workers (path A) involves a 5 step linear sequence to prepare azide **13** from allylic alcohol **14**. The azide is then reduced and cyclized into the advanced intermediate **12**. In our strategy, we planned to elaborate epoxy nitrile **15**

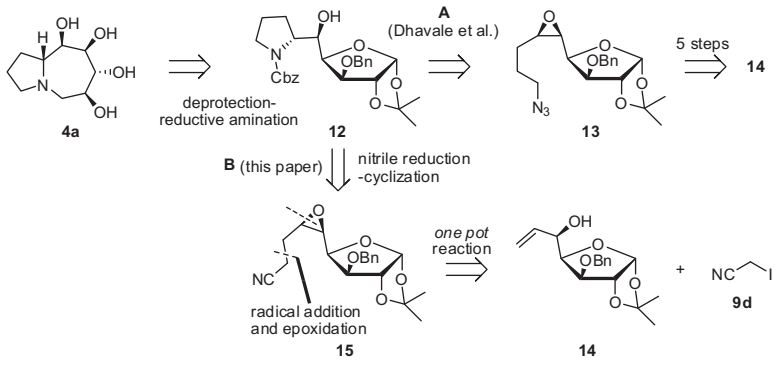
Table 2
Different precursors and alcohols

Entry	Precursor	Alcohol	Product (Yield%)
1	**9a**	**10a**	**11a** (49[a], 78[b], 80[c])
2	 **9b**	**10a**	 **11b** (79%[b], 61%[c])
3	**9a**	 **10b**[d]	 **11c** (77%, 42%[c])
4	 **9c**	**10a**	 **11d** (15%[b], 30%[c])
5	 **9d**	**10a**	 **11e** (83%[b], 67%[c])
6	**9d**	 **10b**	 **11f** (71%[b], 58%[c])
7	**9d**	 **10c**	 **11g** (47%[b], 49%[c])
8	 **9e**	**10a**	 **11h** (0%[b], 30%[c])
9	 **9f**	**10a**	 **11i** (45%[b])
10	 **9g**	**10a**	 **11j**[b,c,e]
11	 **9h**	**10a**	S.M.[b,c,f]
12	 **9i**	**10a**	S.M.[b,c,f]

[a] Conditions A were used.
[b] Conditions B were used.
[c] Conditions C were used.
[d] Compounds **10b**–**d** were prepared by reaction of the corresponding aldehyde with vinylmagnesium bromide according to known procedures.
[e] Only 4-chloroacetophenone (reduced product) was detected after complete consumption of the starting material and addition of 0.3 equiv of Et_3B.
[f] Only starting material was recovered after several hours of reaction.



Scheme 2. Planned route for the synthesis of 2-hydroxypirrolidines.



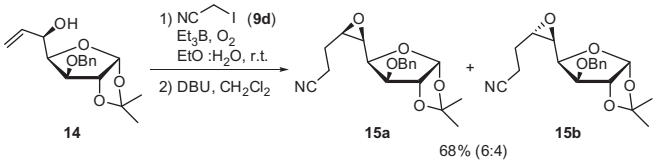
Scheme 3. Described and proposed strategies for the synthesis of perhydroaza-azulene **4a**.

as the key intermediate. The latter could be prepared in a more straightforward manner from alcohol **14** and iodoacetonitrile (**9d**) by applying our radical-ionic sequence and then transformed into pirrolydine **12** by nitrile reduction and epoxide opening.

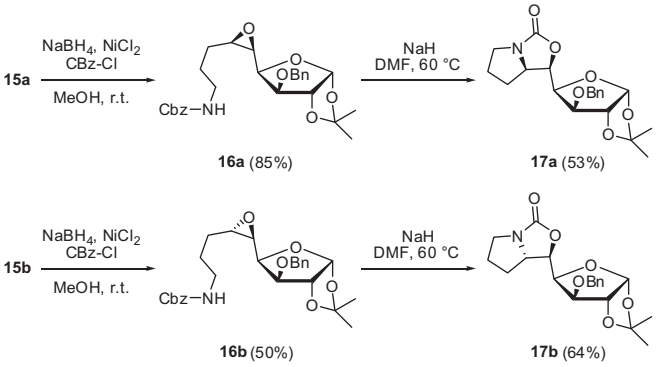
Thus, we started our synthesis by applying the radical addition-epoxidation protocol to a mixture of D-xylofuranose derivative **14** and iodoacetonitrile (**9d**). Surprisingly, with this particular substrate, the radical step only proceeded when method C was used (ethanol–H_2O for the radical step and then DBU in DCM). Under these conditions, a 6:4 diastereoisomeric mixture of **15a** and **15b** was isolated in 68% yield (Scheme 4).

With epoxides **15a**/**15b** in hand, we tested the reduction of the nitrile moiety with different reagents and conditions. Catalytic hydrogenation (H_2/Pd–C) or strong reducing reagents ($LiAlH_4$) only lead to the recovery of the starting material or to a complex mixture of products. After some experimentation, we found that modified Caddick conditions[11] smoothly provided the Cbz carbamates **16a** and **16b** in 85% and 50% yields, respectively (Scheme 5). In order to perform the desired 5-*exo*-*tet* cyclization, a number of methods, such as H_2/Pd–C, $BF_3{\cdot}OEt_2$ or LDA were tested without success. We finally found that when a mixture of **16a** or **16b** and NaH in DMF was heated at 60 °C for 2–8 h, the expected cyclization is performed but with the concomitant attack of the resulting alcoholate over the carbamate, leading to the isolation of cyclic carbamates **17a** (53%) and **17b** (64%). ^{1}H NMR spectra of **17a** matched perfectly with those reported previously.[6] On the other hand, structure of **17b** was unambiguously assigned by X-ray diffraction (Fig. 2).

The final steps of our approach are outlined in scheme 6. First, cyclic carbamate **17a** was opened by means of base treatment to afford the corresponding aminoalcohol which was immediately subjected to Cbz reprotection to afford **18a** in 73% yield (2 steps). Spectral data for compound **18a** fully matched with those reported by Dhavale and co-workers and it could be converted into perhydroaza-azulene **4a** under the reported reaction conditions.[6] Thus, we have achieved a formal total synthesis of **4a**. In the case of **17b**, the same sequence of reactions was applied (carbamate opening and Cbz protection), and **18b** was isolated in 50% yield. Compound **18b** could be transformed into the new perhydroaza-azulene (epimeric at C-6) by applying Dhavale's conditions (as for **18a**).



Scheme 4. Synthesis of epoxides **15a** and **15b**.



Scheme 5. Preparation of cyclic carbamates **17a** and **17b**.

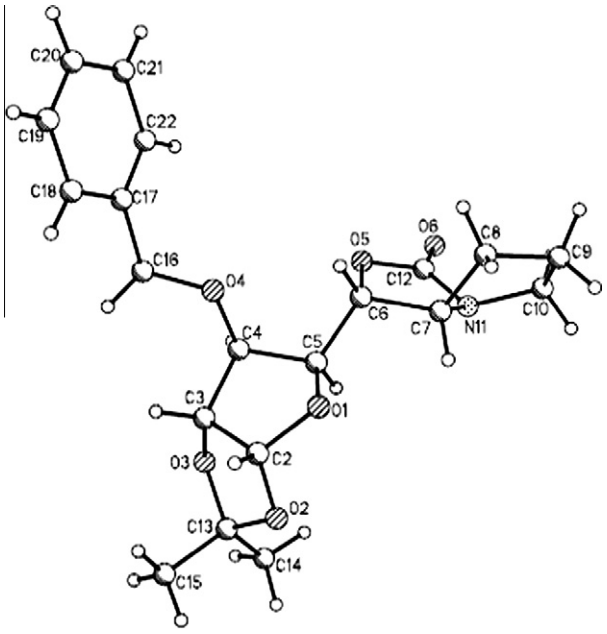
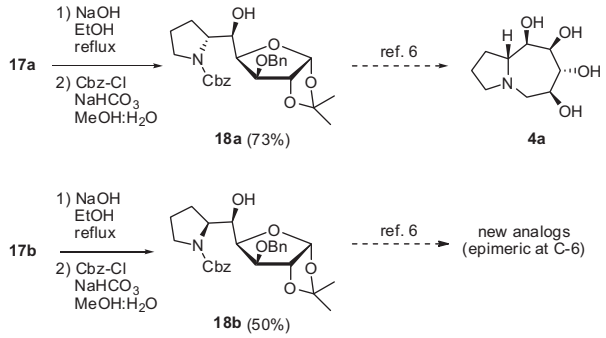


Figure 2. ORTEP drawing of compound **17b**.

In conclusion, we have developed a useful free-radical atom-transfer reaction followed by a base-promoted cyclization that allows the direct obtention of epoxides from α-iodoesters or α-iodonitriles and allylic alcohols. The sequence can be performed in either aqueous or organic solvents, without the use of protective groups and in a *one-pot* fashion, which makes this sequence a very



Scheme 6. Completion of the synthesis of perhydroaza-azulene **4a** and of new compound **18b**.

useful tool in organic synthesis. We have also applied the above-mentioned protocol to the formal synthesis of perhydroaza-azulenes in a straightforward route. Efforts in order to develop a stereoselective version of this protocol as well as the synthesis of other biologically important alkaloids are currently in progress.

Experimental Section

One-pot protocol for the direct preparation of epoxides. (Method B): To a solution of the appropriate radical precursor (1 mmol) and allylic alcohol (2 mmol) in dichloromethane (10 mL) at room temperature was added triethylborane (0.1 mmol of a 1.0 M solution in hexanes). 2 mL of air was then bubbled into the solution and the reaction mixture was allowed to stir at rt. Extra additions of Et_3B (0.1 mmol) and air (2 mL) were done every hour until complete consumption of the starting material. DBU (1.5 mmol) was then added and the reaction was stirred at rt for further 2 h. When the reaction was completed, the solvent was evaporated under reduced pressure and the residue was purified by flash chromatography.

Method C: To a solution of the starting material and allylic alcohol in ethanol/water (10 mL of a 3:1 mixture) was added Et_3B (0.1 mmol of a 1.0 M solution in THF). 2 mL of air was then bubbled into the solution and the reaction mixture was allowed to stir at rt. Extra additions of Et_3B (0.1 mmol) and air (2 mL) were done every hour until complete consumption of the starting material. Ethanol was then evaporated and the reaction extracted with CH_2Cl_2. The organic extracts were dried (Na_2SO_4), filtered, and concentrated in vacuo. The residue was dissolved in 10 mL of dichloromethane and 1.5 mmol of DBU was added to the reaction mixture. When the starting material was completely consumed, the solvent was evaporated off, and the reaction purified by flash column chromatography.

Acknowledgments

We wish to thank Instituto de Química (UNAM), CONACyT (project number 80047) and DGAPA (project number *I*1200511) for generous financial support. E. Peralta-Hernández and O. Cortezano-Arellano also thank CONACyT for graduate scholarships (grants number 23553 and 162040). We also thank Angeles Peña and Isabel Chavez-Uribe for technical support (NMR).

Supplementary data

Supplementary data (experimental procedures, spectroscopic data for new compounds, and data for X-ray diffraction of compound **16b**) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.10.042.

References and notes

1. (a) Hohenschutz, L. D.; Bell, E. A.; Jewess, P. J.; Leworthy, D. P.; Pryce, R. J.; Arnold, E.; Clardy, J. *Phytochemistry* **1981**, *20*, 811; (b) Nash, R. J.; Fellows, L. E.; Dring, J. V.; Stirton, C. H.; Carter, D.; Hegarty, M. P.; Bell, E. A. *Phytochemistry* **1988**, *27*, 1403.
2. (a) Guennguerich, F. P.; DiMari, S. J.; Broquist, H. P. *J. Am. Chem. Soc.* **1973**, *95*, 2055; For a review on the synthesis of swainsonine and lentiginosine, see: (b) Nemr, A. E. *Tetrahedron* **2000**, *56*, 8579; For a recent synthesis, see: (c) Chooprayoon, S.; Kuhakarn, C.; Tuchinda, P.; Reutrakul, V.; Pohmaktor, M. *Org. Biomol. Chem.* **2011**, *9*, 531.
3. (a) Pastuszak, I.; Molyneux, R. J.; James, L. F.; Elbein, A. D. *Biochemistry* **1990**, *29*, 1886; (b) Michael, J. P. *Nat. Prod. Rep.* **2001**, *18*, 520.
4. For reviews on polyhydroxylated alkaloids, see: (a) Sears, P.; Wong, C.-H. *Angew. Chem., Int. Ed.* **1999**, *38*, 2300; (b) Chen, Y.; Vogel, P. *J. Org. Chem.* **1994**, *59*, 2487; (c) Michael, J. *Nat. Prod. Rep.* **2004**, *21*, 625.
5. (a) Burguess, K.; Henderson, I. *Tetrahedron* **1992**, *48*, 4045; (b) Markad, S. D.; Karanjule, N. S.; Sharma, T.; Sabharwal, S. G.; Dhavale, D. D. *Org. Biomol. Chem.* **2006**, *4*, 3675; (c) Kumar, K. S. A.; Chaudhari, V. D.; Dhavale, D. D. *Org. Biomol. Chem.* **2008**, *6*, 703; (d) Wang, N.; Zhang, L.-H.; Ye, X.-S. *Org. Biomol. Chem.* **2010**, *8*, 2639.
6. Markad, S. D.; Karanjule, N. S.; Sharma, T.; Sabharwal, S. G.; Puranik, V. G.; Dhavale, D. D. *Org. Biomol. Chem.* **2006**, *4*, 2549.
7. (a) Byers, J. In *Radicals in Organic Synthesis*; Renaud, P., Sibi, M. P., Eds.; Wiley-VCH: Weinheim, 2001; pp 72–89; Atom transfer radical reactions can also be catalyzed by Cu(I). For a review, see: (b) Eckenhoff, W. T.; Pintauer, T. *Cat. Rev.* **2010**, *52*, 1.
8. Yorimitsu, H.; Nakamura, T.; Shinokubo, H.; Oshima, K.; Omoto, K.; Fujimoto, H. *J. Am. Chem. Soc.* **2000**, *122*, 11041.
9. (a) Nozaki, K.; Oshima, K.; Utimoto, K. *Bull. Chem. Soc. Jpn.* **1991**, *64*, 403; (b) Horiuchi, Y.; Taniguchi, M.; Oshima, K.; Utimoto, K. *Tetrahedron Lett.* **1995**, *36*, 5353; (c) Chandrasekhar, S.; Narsihmulu, C.; Reddy, N.; Reddy, S. *Tetrahedron Lett.* **2003**, *44*, 2583.
10. (a) Giese, B. *Angew. Chem., Int. Ed.* **1983**, *22*, 753; (b) Tedder, J. M.; Walton, J. C. *Acc. Chem. Res.* **1976**, *9*, 183.
11. Caddick, S.; Judd, D. B.; Lewis, A. K. K.; Reich, M. T.; Williams, R. V. *Tetrahedron* **2003**, *59*, 5417.