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Highly efficient synthesis of phenanthroquinolizidine alkaloids via Parham-type cycliacylation

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ABSTRACT

A concise and efficient route involving Parham-type cycliacylation as the key step has been used to synthesize phenanthroquinolizidine alkaloids **1a–c** and **2a–c**. Among the products, **1b**-(***S***), **1b**-(***R***), **2a**-(**14a*S*,15*S***), **2a**-(**14a*R*,15*R***), and **2b** were synthesized for the first time.

Phenanthroquinolizidine alkaloids are a small group of alkaloids existing in the *Lauraceae*, *Vitaceae*, and *Urticaceae* families of plants. Only five of these alkaloids (−)-cryptopleurine **[1c**-(***R***)], boehmeriasin A [**1b**-(***dl***)], boehmeriasin B (Fig. 1), (−)-(15*R*)-hydroxycryptopleurine [**2c**-(**14a*R*,15*R***)], and cryptopleuridine (Fig. 1) have been isolated by now.[1] It has been reported that these alkaloids possess unique and interesting biological properties including vesicant, antimicrobial, antiviral, and anticancer activities.[1a,j–l,2] We have previously reported that these alkaloids possess excellent antiviral activity against the tobacco mosaic virus (TMV).[3] To extend our research on phenanthroquinolizidine alkaloids as antiviral agents, we developed an efficient approach to the preparation of racemic alkaloids.[4] Now to further explore the effect of the α-C chirality on antiviral activity, a series of enantiopure phenanthroquinolizidine alkaloids need to be tested.

So far, only a few members of these alkaloids have been synthesized selectively using the chiron approach or the chiral auxiliary approach.[5] However, these reported approaches are not suitable for large-scale preparation due to low yields, harsh conditions, or the many steps required.

Furthermore, the construction of the phenanthrene and quinolizidine nuclei always plays a key role in the synthesis of phenanthroquinolizidine alkaloids. In our previous work, $FeCl_3$ was used as the oxidative coupling reagent to construct the phenanthrene nucleus efficiently.[6] We then directed our attention toward the construction of quinolizidine nucleus. In the last five decades, the most commonly reported synthetic methodology for the construction of this structure was the acid-catalyzed cyclization of an amino-acid.[5a,b,7] However, in each case, racemic products and low yields resulted due to the harsh conditions employed for ring closure.

On the other hand, the intramolecular cyclization reactions that employ aryllithiums generated by lithium–halogen exchange, known as Parham cyclization reactions, have become a valuable protocol for the regiospecific construction of carbocyclic and heterocyclic systems.[8] Inspired by the methodology of Lete and coworkers,[8g,i] this aromatic metalation–cyclization procedure has been successfully used to prepare the quinolizidine nucleus of phenanthroquinolizidine alkaloids. In these cases, the unstable ketone intermediates (Fig. 2) were directly reduced to corresponding alcohols **2a–c** to avoid decomposition. In this Letter, we report full details of this synthetic approach to phenanthroquinolizidine alkaloids.

The synthetic strategy for the construction of phenanthroquinolizidine alkaloids **1a–c** and **2a–c** is depicted in Figure 2. Firstly, the

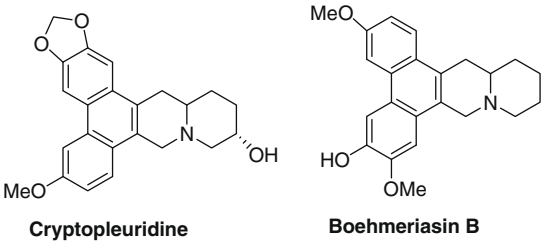

Figure 1. Chemical structures of cryptopleuridine and boehmeriasin B.

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dibromides **5**, formed by dibromination reaction of alcohols **4**, underwent a N-alkylation reaction to yield amides **6**. Secondly, the amides **6** proceeded through metalation–cyclization–reduction sequences to afford alcohols **2**. At last, hydride reduction gave the target products **1**.

The synthetic route to phenanthroquinolizidines **1a–c** and **2a–c** is illustrated in Scheme 1. The ester **3a**[6] was treated with lithium aluminum hydride to give alcohol **4a** in 96% yield. It has been reported that polymethoxylated benzyl alcohols can be converted into the corresponding dibromides in excellent yields in one step.[9] By using this procedure, **4a** was successfully converted into dibromide **5a** in 92% yield, thus improving the results previously reported by Ishibashi and co-workers.[10] (*S*)-*N*,*N*-diethylpiperidine-2-carboxamide [**7**-(***S***)][11] was alkylated with **5a** to

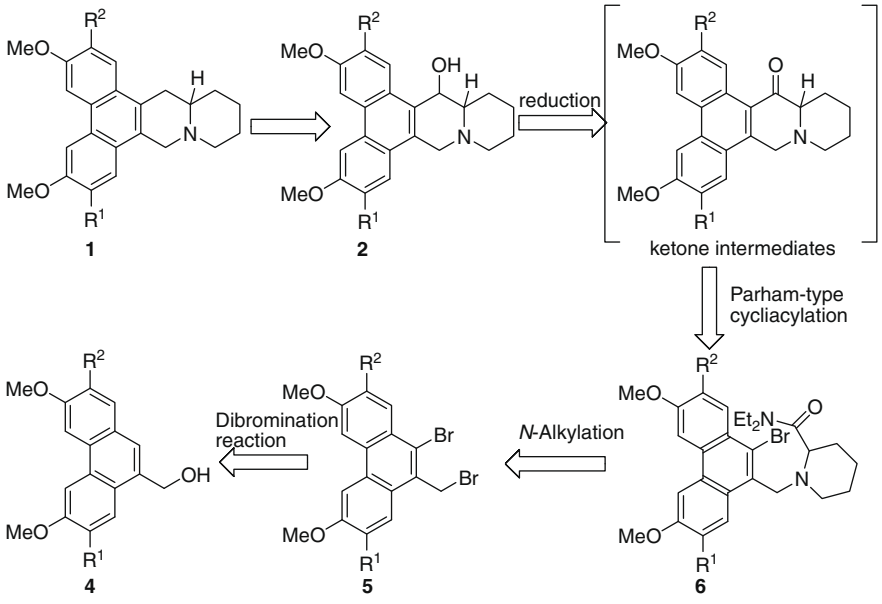
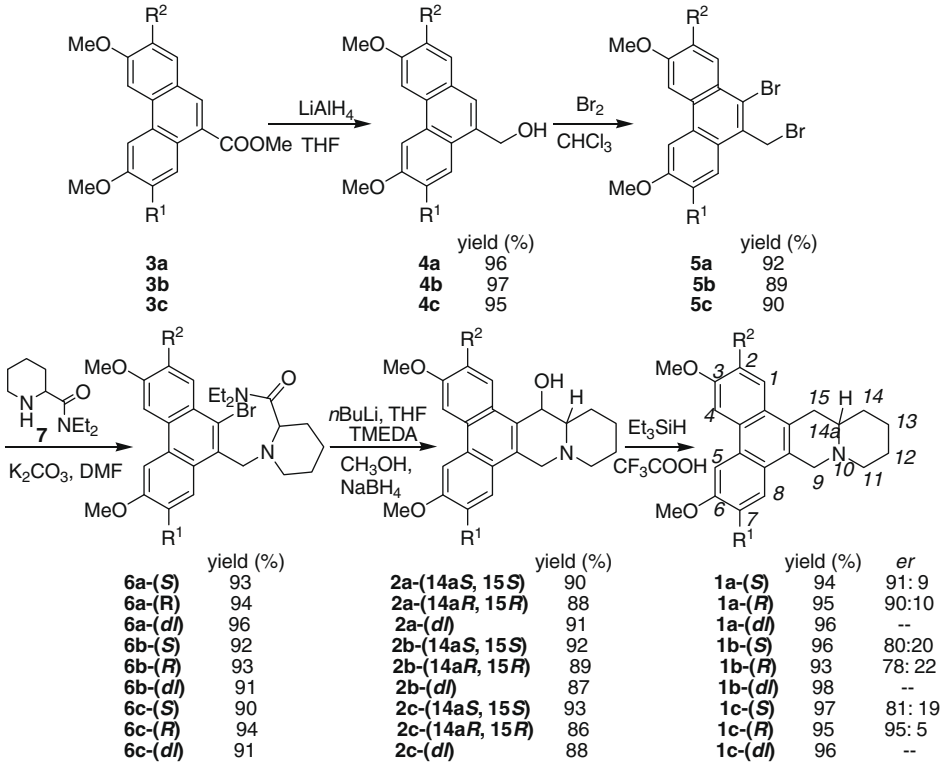


Figure 2. Retrosynthetic analysis.



a: $R^1 = R^2 = OCH_3$; b: $R^1 = OCH_3$, $R^2 = H$; c: $R^1 = H$, $R^2 = OCH_3$

Scheme 1. Synthesis of phenanthroquinolizidine alkaloids **1a–c** and **2a–c**.

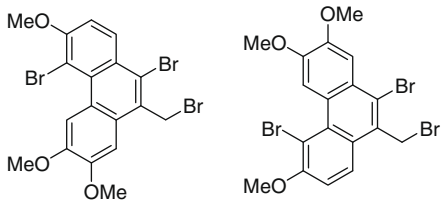


Figure 3. Chemical structures of **5d** and **5e**.

produce amide **6a**-(***S***) in 93% yield. After metalation–cyclization–reduction sequences, **6a**-(***S***) was successfully converted into (+)-7-methoxy-(15*S*)-hydroxycryptopleurine [**2a**-(**14a*S*,15*S***)] in 90% yield. **2a**-(**14a*S*,15*S***) was reduced using triethylsilane and trifluoroacetic acid to give (+)-7-methoxycryptopleurine [**1a**-(***S***)] in 94% yield. When using **7**-(***R***)[11] instead of **7**-(***S***), (−)-7-methoxycryptopleurine [**1a**-(***R***)] was obtained by the same procedure in 69% overall yield.

Although a similar approach seemed directly applicable to the preparation of **1b**–**c**, differences were immediately noted. Reduction of **3b**–**c** with lithium aluminum hydride afforded the corresponding alcohols **4b**–**c**. When **4b** was treated with bromine under above-mentioned conditions, dibromide **5b** was obtained accompanied by a small percentage of tribromide **5d** (Fig. 3). The ^{1}H NMR spectrum of **5d** indicated that the additional bromine was located at the 5-position. To avoid the tribromination, **4b** was treated with bromine below −5 °C for 5 h, then stirred at 10 °C for another 10 h. After this, dibromide **5b** was obtained in 89% yield. **7**-(***S***) was alkylated with **5b** to produce amide **6b**-(***S***) in 92% yield. After metalation–cyclization–reduction sequences, **6b**-(***S***) was converted into (+)-(15*S*)-hydroxyboehmeriasin A [**2b**-(**14a*S*,15*S***)] in 92% yield. **2b**-(**14a*S*,15*S***) was reduced using triethylsilane and trifluoroacetic acid to give (+)-boehmeriasin A [**1b**-(***S***)] in 96% yield. By using the same methodology, (−)-boehmeriasin A [**1b**-(***R***)], (+)-cryptopleurine [**1c**-(***S***)], and (−)-cryptopleurine [**1c**-(***R***)] were obtained in 66%, 69%, and 66% overall yields, respectively.

The racemates (±)-7-methoxycryptopleurine [**1a**-(***dl***)], (±)-boehmeriasin A [**1b**-(***dl***)], and (±)-cryptopleurine [**1c**-(***dl***)] were also synthesized by using the same synthetic methodology in 74%, 67%, and 66% overall yields, respectively.

It should be noted that the er ratios of alkaloids **1a**–**c** range from 78:22 to 95:5, although the same synthetic methodology and commercially available enantiopure 2-piperidinecarboxylic acid were used. The partial racemization was most possibly due to the unstable intermediates **2a**–**c**. Similar results were also reported by Buckley III and Rapoport.[5b]

In summary, a short and efficient route to phenanthroquinolizidine alkaloids has been accomplished with Parham-type cycliacylation as the key step. This new procedure has distinct advantages over the previous ones: it is simple and practical, allowing a series of phenanthroquinolizidine alkaloids to be prepared on a large scale, it involves few steps, and high overall yields. As a result of the flexibility and robust character of this approach, a systematic exploration of the pharmacological profile of this promising class of bioactive natural products may be possible.

Acknowledgments

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Supplementary data

Supplementary data (complete experimental procedures and spectroscopic data for **4a**–**c**, **5a**–**e**, **6a**-(***S***), **6b**-(***S***), **6c**-(***S***), **2a**-(**14a*S*,15*S***), **2b**-(**14a*S*,15*S***), **2c**-(**14a*S*,15*S***) and **1a**–**c**) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.12.135.

References and notes

1. (a) Lande, D. E. *Aust. J. Exp. Biol. Med. Sci.* **1948**, *34*, 181–187; (b) Gellert, E.; Riggs, N. V. *Aust. J. Chem.* **1954**, *7*, 113–120; (c) Gellert, E. *Aust. J. Chem.* **1956**, *9*, 489–496; (d) Hart, N. K.; Johns, S. R.; Lamberton, J. A. *Aust. J. Chem.* **1968**, *21*, 1397–1398; (e) Hart, N. K.; Johns, S. R.; Lamberton, J. A. *Aust. J. Chem.* **1968**, *21*, 2579–2581; (f) Farnsworth, N. R.; Hart, N. K.; Johns, S. R.; Lanberton, J. A.; Messmer, W. *Aust. J. Chem.* **1969**, *22*, 1805–1807; (g) Hoffman, J. J.; Luzbetak, D. J.; Torrance, S. J.; Cole, J. R. *Phytochemistry* **1978**, *17*, 1448; (h) Gellert, E.; Richard, R.; Craig, J. C.; Roy, S. K.; Woodard, R. W. *Aust. J. Chem.* **1978**, *31*, 2095–2097; (i) Saifah, E.; Kelley, C. J.; Lear, J. D. *J. Nat. Prod.* **1983**, *46*, 353–358; (j) Luo, Y.; Liu, Y.; Luo, D.; Gao, X.; Li, B.; Zhang, G. *Planta Med.* **2003**, *69*, 842–845; (k) Luo, Y.; Liu, Y.; Luo, D.; Gao, X.; Li, B.; Zhang, G. CN 1463973, 2003 (CAN 2005, 142: 385974).; (l) Cai, X. F.; Jin, X. J.; Lee, D.; Yang, Y. T.; Lee, K.; Hong, Y. S.; Lee, J. H.; Lee, J. J. *J. Nat. Prod.* **2006**, *69*, 1095–1097.
2. (a) Donaldson, G. R.; Atkinson, M. R.; Murray, A. W. *Biochem. Biophys. Res. Commun.* **1968**, *31*, 104–109; (b) Krmpotic, E.; Farnsworth, N. R.; Messmer, W. M. *J. Pharm. Sci.* **1972**, *61*, 1508–1509; (c) Al-Shamma, A.; Drake, S. D.; Guagliardi, L. E.; Mitscher, L. A.; Swayze, J. K. *Phytochemistry* **1982**, *21*, 485–487; (d) Michael, J. P. *Nat. Prod. Rep.* **2005**, *22*, 603–626; (e) Banwell, M. G.; Bezos, A.; Burns, C.; Kruszeknicki, I.; Parish, C. R.; Su, S.; Sydnes, M. O. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 181–185; (f) Gao, W. L.; Chen, A. P. C.; Leung, C. H.; Gullen, E. A.; Fürstner, A.; Shi, Q.; Wei, L.; Lee, K. H.; Cheng, Y. C. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 704–709.
3. Wang, Q. M.; Wang, K. L.; Huang, Z. Q.; Liu, Y. X.; Li, H.; Hu, T. S.; Jin, Z.; Fan, Z. J.; Huang, R. Q. CN 101189968, CAN 2008, 149: 97630.
4. Cui, M. B.; Wang, Q. M. *Eur. J. Org. Chem.* **2009**, *31*, 5445–5451.
5. (a) Foldeak, S. *Tetrahedron* **1971**, *27*, 3465–3476; (b) Buckley, T. F., III; Rapoport, H. *J. Org. Chem.* **1983**, *48*, 4222–4232; (c) Suzuki, H.; Aoyagi, S.; Kibayashi, C. *J. Org. Chem.* **1995**, *60*, 6114–6122; (d) Suzuki, H.; Aoyagi, S.; Kibayashi, C. *Tetrahedron Lett.* **1995**, *36*, 935–936; (e) Kim, S.; Lee, T.; Lee, E.; Lee, J.; Fan, G.; Lee, S.; Kim, D. *J. Org. Chem.* **2004**, *69*, 3144–3149.
6. Wang, K. L.; Lü, M. Y.; Yu, A.; Zhu, X. Q.; Wang, Q. M. *J. Org. Chem.* **2009**, *74*, 935–938.
7. (a) Marchini, P.; Belleau, B. *Can. J. Chem.* **1958**, *36*, 581–588; (b) Trigo, G. G.; Galvez, E.; Sollhuber, M. M. *J. Heterocycl. Chem.* **1980**, *17*, 69–72.
8. (a) Bradsher, C. K.; Hunt, D. A. *J. Org. Chem.* **1981**, *46*, 327–330; (b) Parham, W. E.; Bradsher, C. K. *Acc. Chem. Res.* **1982**, *15*, 300–305; (c) Collado, M. I.; Lete, E.; Sotomayor, N.; Villa, M. J. *Tetrahedron* **1995**, *51*, 4701–4710; (d) Collado, M. I.; Sotomayor, N.; Villa, M. J.; Lete, E. *Tetrahedron Lett.* **1996**, *37*, 6193–6196; (e) Collado, M. I.; Manteca, I.; Sotomayor, N.; Villa, M. J.; Lete, E. *J. Org. Chem.* **1997**, *62*, 2080–2092; (f) Ardeo, A.; Lete, E.; Sotomayor, N. *Tetrahedron Lett.* **2000**, *41*, 5211–5214; (g) Ruiz, J.; Sotomayor, N.; Lete, E. *Org. Lett.* **2003**, *5*, 1115–1117; (h) Moreau, A.; Couture, A.; Deniau, E.; Grandclaudon, P. *Eur. J. Org. Chem.* **2005**, *16*, 3437–3442; (i) Ruiz, J.; Ardeo, A.; Ignacio, R.; Sotomayor, N.; Lete, E. *Tetrahedron* **2005**, *61*, 3311–3324; (j) Ruiz, J.; Lete, E.; Sotomayor, N. *Tetrahedron* **2006**, *62*, 6182–6189; (k) Lamblin, M.; Couture, A.; Deniau, E.; Grandclaudon, P. *Tetrahedron* **2007**, *63*, 2664–2669.
9. (a) Dai-Ho, G.; Mariano, P. S. *J. Org. Chem.* **1987**, *52*, 706–707; (b) Cochran, J. E.; Padwa, A. *J. Org. Chem.* **1995**, *60*, 3938–3939; (c) Olivera, R.; SanMartin, R.; Domínguez, E.; Solans, X.; Urtiaga, M. K.; Arriortua, M. I. *J. Org. Chem.* **2000**, *65*, 6398–6411; (d) Harrowven, D. C.; Nunn, M. I. T.; Blumire, N. J.; Fenwick, D. R. *Tetrahedron Lett.* **2000**, *41*, 6681–6683; (e) Harrowven, D. C.; Sutton, B. J.; Coulton, S. *Tetrahedron Lett.* **2001**, *42*, 2907–2910.
10. Takeuchi, K.; Ishita, A.; Matsuo, J.; Ishibashi, H. *Tetrahedron* **2007**, *63*, 11101–11107.
11. Vecchietti, V.; Giordani, A.; Giardina, G.; Colle, R.; Clarke, G. D. *J. Med. Chem.* **1991**, *34*, 397–403.