Bridgehead Arylation: A Direct Route to Advanced Intermediates for the Synthesis of C-20 Diterpene Alkaloids

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Received July 16, 2003

ABSTRACT



Rapid access to the ABCE ring system of the C20 diterpene alkaloids was achieved by silver(I)-promoted intramolecular Friedel-Crafts arylation of a functional group-specific 5-bromo-3-azabicyclo[3.3.1]nonane derivative.

Diterpene alkaloids are distributed widely throughout the plant world and have been isolated from a variety of genera (Aconitum, Delphinium, Consolida, Thalictrum, and Spiraea).^{1,2} Although these alkaloids display a range of biological activity,³ it is their structurally congested skeletons that have attracted and continue to command considerable interest from natural product^{4,5} and synthetic⁶ chemists. Over a period of two to three decades, the Wiesner group reported an

(2) Pelletier, S. W.; Mody, N. V. In The Alkaloids; Manske, R. H. F., Rodrigo, R. G. A., Eds.; Academic Press: New York, 1981; Vol. 18, pp 99-216. (b) Wang, F.-P.; Liang, X.-T. In The Alkaloids; Cordell, G. A., Ed.; Academic Press: New York, 1992; Vol. 42, pp 151-247.

(3) Jacyno, J. M. In Chemistry and Toxicology of Diverse Classes of Alkaloids; Blum, M., Ed.; Alaken, Inc.: Ft. Collins, CO, 1996; p 301.

(4) Selection of recent reports: Mericli, A. H.; Mericli, F.; Seyhan, G. V.; Bahar, M.; Desai, H. K.; Ozcelik, H.; Ulubelen, A. Pharmazie 2002, *57*, 761–762. (b) Wang, F.-P.; Peng, C.-S.; Yu, K.-B. *Tetrahedron* **2000**, *56*, 7443–7446. (c) He, H.-P.; Shen, Y.-M.; Zhang, J.-X.; Zuo, G.-Y.; Hao, X.-J. J. Nat. Prod. 2001, 64, 379-380. (d) Grandez, M.; Madinaveitia, A.; Gavín, J. A.; Alva, A.; de la Fuente, G. J. Nat. Prod. 2002, 65, 513-516. (e) Saidkhodzhaeva, Sh. A.; Bessonova, I. A.; Abdullaev, N. D. Chem. Nat. Compd. 2001, 37, 466-469.

(5) Selection of recent reports: (a) Xu, L.; Chen, Q.-H.; Wang, F.-P. Tetrahedron 2002, 58, 4267-4271. (b) Chen, Q.-H.; Xu, L.; Wang, F.-P. Tetrahedron 2002, 58, 9431-9444. (c) Wang, F.-P. Chen, Q.-H.; Li, Z.-B.; Li, B.-G. Chem. Pharm. Bull. 2001, 49, 689-694.

extraordinary series of biogenetically modeled total syntheses of the more complex C₁₉ derivatives as well as a number of related C₂₀ analogues.⁷ Equally creative endeavors leading to the simpler C₂₀ alkaloids have been described by Masamune,8 Fukumoto,9 and Nagata.10 The highly bridged structure of the kobusine¹¹ (1)-hetisine¹² (2) family¹³ of alkaloids (Figure 1) also poses an alluring target for synthetic chemists, prompting the development of ingenious strategies and new methodology.14-16 These recent reports prompted us to

ORGANIC LETTERS

2003Vol. 5, No. 19

3499-3502

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⁽¹⁾ Pelletier, S. W.; Page, S. W. Nat. Prod. Rep. 1986, 3, 451-475. (b) Yunusov, M. S. Nat. Prod. Rep. 1993, 10, 471-486. (c) Atta-ur-Rahman; Choudhary, M. I. Nat. Prod. Rep. 1999, 16, 619-635.

⁽⁶⁾ Barker, D.; McLeod, M. D.; Brimble, M. A.; Savage, G. P. Tetrahedron Lett. 2002, 43, 6019-6022. (b) Barker, D.; Brimble, M. A.; McLeod, M. D.; Savage, G. P.; Wong, D. J. J. Chem. Soc., Perkin Trans. 1 2002, 924-931. (c) Baillie, L. C.; Bearder, J. R.; Whiting, D. A. J. Chem. Soc., Chem. Commun. 1994, 2487-2488. (d) Kraus, G. A.; Dneprovskaia, E. Tetrahedron Lett. 1998, 39, 2451-2454.

⁽⁷⁾ Wiesner, K. Tetrahedron 1985, 41, 485-497.

⁽⁸⁾ Masamune, S. J. J. Am. Chem. Soc. 1964, 86, 291.

^{(9) (}a) Ihara, M.; Suzuki, M.; Fukumoto, K.; Kametani, T.; Kabuto, C. J. Am. Chem. Soc. **1988**, 110, 1963–1964. (b) Ihara, M.; Suzuki, M.; Fukumoto, K.; Kabuto, C. J. Am. Chem. Soc. **1990**, 112, 1164–1171.

⁽¹⁰⁾ Nagata, W.; Narisada, M.; Wakabayashi, T.; Sugasawa, T. J. Am.

Chem. Soc. 1967, 89, 1499-1504 and references therein. (11) Okamoto, T.; Natsume, M.; Zenda, H.; Kamata, S. Chem. Pharm. Bull. 1962, 10, 883.

⁽¹²⁾ Varughese, K. I.: Pelletier, S. W. J. Nat. Prod. 1984, 47, 470-473. (13) Bessonova, I. A.; Saidkhodzhaeva, Sh. A. Chem. Nat. Compd. 2000, 36, 419-477.

⁽¹⁴⁾ Kwak, Y.-S.; Winkler, J. D. J. Am. Chem. Soc. 2001, 123, 7429-7430.

⁽¹⁵⁾ Muratake, H.; Natsume, M. Tetrahedron Lett. 2002, 43, 2913-2917.



Figure 1. Kobusine and Hetisine.

disclose our own endeavors in the field, which have been undertaken with due regard to the logistical challenges that were likely to develop in pursuing a target possessing such a complex skeleton.

We were attracted to the bridgehead arylation-based approach attempted by Shimizu et al.,¹⁷ who prepared 3-methyl-9-(4-methoxyphenylethyl)-3-azabicyclo[3.3.1]nonan-9-ol **3** but were unable to convert it into the target phenanthrene derivative **4** (Scheme 1). (Equivalent, but



simpler arene carbinols have been cyclized to give hydrophenanthrenes, presumably via alkene formation or a 1,2hydride shift to give the isomeric cation.¹⁸ In this case, however, the formation of the necessary bridgehead alkene or cation violates Bredt's rule.¹⁹)

The rapid assembly of 3-azabicyclo[3.3.1]nonan-7-ones by means of a double Mannich reaction on cyclohexanone-based starting materials²⁰ nevertheless provides a particularly direct and efficient method for establishing a platform for further elaboration. A further major element in our planned approach was the utilization of a suitably functionalized aromatic C-ring that would serve as a precursor to an *ortho*-quinonoid moiety in anticipation of the addition of the D-ring by means of a [4 + 2] cycloaddition, a tactic that has been used very effectively by Wiesner.²¹ If we could combine these elements into a viable strategy, there was then a reasonable expectation of restricting the complete sequence to a manageable length.

(20) Blicke, F. F.; McCarty, F. J. J. Org. Chem. 1959, 24, 1379-1380.

To address the problem of the intramolecular arylation that had eluded Shimizu et al., we elected to begin with the bromo-3-azabicyclo[3.3.1]nonanone **5** (the *N*-methyl analogue of an intermediate that had been prepared previously by Kraus and Shi²²) with the knowledge that intermolecular bridgehead arylation had been achieved with 1-bromoadamantane using palladium (Pd/C) at high temperature (de Meijere²³) and with 1-bromobicyclo[2.2.2]octane using silver(I) salts at room temperature (Kraus²⁴). Thus, we arrived at the synthetic plan outlined in Scheme 2 and now describe its successful execution as far as the tetracycle **6**.



The arylacetylene 7^{25} was synthesized in three steps from *ortho*-vanillin in good overall yield, using Corey–Fuchs methodology.²⁶ Masking by the robust isopropyl ether function as developed by Banwell²⁷ was chosen so as to allow for selective dealkylation at the appropriate juncture without the risk of premature deprotection. Deprotonation of arylacetylene **7** with methylmagnesium bromide and subsequent reaction with bicycle **5** dissolved in toluene afforded a 3:2 mixture of diastereomers **8** and **9** in 94% yield. With THF as a solvent, however, mainly the desired epimer²⁸ **8** (64% yield) was obtained, accompanied this time by the byproduct **10** from rearrangement of **9** (Scheme 3). This kind of rearrangement had also been observed by Kraus and put to good effect in the synthesis of *epi*-modhephene.²²

Reduction of the alkyne bond with retention of the bridgehead bromo substitutent was always going to be a concern, but reaction of **8** with diimide, generated in situ from 1,3,5triisopropylbenzene-sulfonylhydrazide,²⁹ afforded the *cis*-

(27) Banwell, M. G.; Flynn, B. L.; Stewart, S. G. J. Org. Chem. 1998, 63, 9139-9144.

⁽¹⁶⁾ van der Baan, J. L.; Bickelhaupt, F. Recl. Trav. Chim. Pays-Bas. 1975, 94, 109-112.

⁽¹⁷⁾ Shimizu, B.; Ogiso, A.; Iwai, I. Chem. Pharm. Bull. 1963, 11, 766–769.

 ⁽¹⁸⁾ Floyd, A. J.; Dyke, S. F.; Ward, S. E. Chem. Rev. 1976, 76, 509.
 (19) Warner, P. M. Chem. Rev. 1989, 89, 1067-1093.
 (20) Dirich, F. E. McGerri, F. L. Q. S. Chem. 1980, 214, 1270, 1280.

^{(21) (}a) Sethi, S. P.; Sterzycki, R.; Sy, W. W.; Marini-Bettolo, R.; Tasai, T. Y. R.; Wiesner, K. *Heterocycles* **1980**, *14*, 23–28. (b) Wiesner, K. *Pure Appl. Chem.* **1979**, *51*, 689–703 and references therein.

⁽²²⁾ Kraus, G. A.; Shi, J. J. Org. Chem. 1990, 55, 5423-5424.

⁽²³⁾ Bräse, S.; Waegell, B.; de Meijere, A. Synthesis 1998, 148-152 and references therein.

⁽²⁴⁾ Kraus, G. A.; Hon, Y.-S.; Thomas, P. J.; Laramay, S.; Liras, S.; Hanson, J. Chem. Rev. **1989**, 89, 1591.

⁽²⁵⁾ Williams, C. M.; Mander, L. N.; Bernhardt, P. V. Acta Crystallogr. 2003, *E59*, 0561–0563.

⁽²⁶⁾ Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.* **1972**, 3769–3772.

⁽²⁸⁾ Increasing the concentration of the tetrahydrofuran solution can give rise to formation of the undesired diasteroisomer but in no more than 10-15%.







Figure 2. First attempt at bridgehead arylation.

alkene **11** in 74% yield as the sole product (Figure 2). It was hoped that the *cis* stereochemistry of the alkene bond in **11** would reduce the degrees of freedom relative to the saturated analogue and maximize the chances of the planned cyclization. Treatment of **11** with silver trifluoroacetate at various temperatures or with palladium (Pd/C), however, resulted in rearrangement³⁰ to ketone **12** (Figure 2).

Although, acylation of the hydroxyl group could be expected to retard the rearrangement, this simple step proved to be surprisingly difficult.

Nevertheless, when **8** was treated with acetic anhydride and trimethylsilyl triflate, the desired acylation was achieved. While replacement of the isopropyloxy function by acetate also occurred (Scheme 4), it was considered to be of no significance. Nevertheless, partial hydrogenation (this time over Pd/BaSO₄) and treatment of the product **13** with silver trifluoroacetate still led to rearrangement, affording the ketone corresponding to **10**.

Further modification of the functionality in these intermediates by routine procedures to afford substrates 14-17(Figure 3) and subsequent treatment with silver trifluoroacetate still failed to result in cyclization, affording only rearranged products.

However, when both the ester and isopropyl functionalities were modified, i.e., as in diacetate **18**, intramolecular arylation induced by treatment with silver trifluoroacetate was at last observed, producing **19**, albeit it in only 18% yield, the remainder consisting of the rearranged product **20** Scheme 4^a



^a Reagents: (a) TMSOTf/Ac₂O/CH₃CN; (b) Pd/BaSO₄/H₂.



Figure 3. Substrates (14-17) probed for bridgehead arylation.

(Scheme 5). Then, after extensive experimentation with different solvents and silver salts [e.g., AgOCOCF₃, AgBF₄, AgB(C₆F₅)₄³¹], we found that the yield of cyclization could be increased to 53% using silver 2,4,6-trinitrobenzene-sulfonate³² in nitromethane.

⁽²⁹⁾ Cusack, N. J.; Reese, C. B.; Risius, A. C.; Roozpeikar, B. Tetrahedron 1976, 32, 2157–2162.

⁽³⁰⁾ Gambacorta, A.; Turchetta, S.; Bovicelli, P. *Tetrahedron* **1991**, *47*, 9097–9102.

⁽³¹⁾ Mukaiyama, T.; Maeshima, H.; Jona, H. Chem. Lett. 2001, 388–389.



Thus, we believe that we have demonstrated that intramolecular bridgehead arylation affords a viable route to highly functionalized, advanced intermediates, the brevity of the route (the longest linear sequence consists of only eight steps) compensating for the modest yield of cyclization. Current studies are focused on further modification of functionality

(32) Pettitt, D. J.; Helmkamp, G. K. J. Org. Chem. 1964, 29, 2702–2706.

and investigating the surprising sensitivity of the cyclization to what would appear to be peripheral factors.³³ While the kobusine family of alkaloids (>100 in number¹³) remain our main objective, we note that **19** and its analogues may also have the potential to serve as intermediates for the synthesis of denudatine-³⁴ and dictysine-type³⁵ alkaloids.

Acknowledgment. The authors thank the following people for their assistance with this body of research: Prof. M. Bennet (Australian National University) and Prof. L. Gahan (University of Queensland) for respective discussions related to heterogeneously catalyzed hydrogenation and silver ion complexation, Dr. Tri Le for performing NMR analysis, and Mr. Graham McFarlane for mass spectroscopy.

Supporting Information Available: Experimental procedures, characterization data, and copies of ¹H and ¹³C NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0353060

⁽³³⁾ Full report detailing solid-state and solution studies will be presented in due course.

⁽³⁴⁾ Götz, M.; Wiesner, K. *Tetrahedron Lett.* **1969**, 4369–4372.
(35) Salimov, B. T.; Yunusov, M. S.; Rashkes, Ya. V.; Yunusov, S. Yu.

⁽³⁵⁾ Salimov, B. 1.; Yunusov, M. S.; Rashkes, Ya. V.; Yunusov, S. Yu. *Khim. Prir. Soedin.* **1979**, 812–817.