Tetrahedron Letters 54 (2013) 5489–5491

Contents lists available at ScienceDirect

Tetrahedron Letters

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

Bidirectional synthesis of montamine analogs

Melanie B. Freitas, Kelly A. Simollardes, Caroline M. Rufo, Chantel N. McLellan, Gabrielle J. Dugas, Leslie E. Lupien, Elizabeth A. Colby Davie *

Assumption College, 500 Salisbury Street, Worcester, MA 01609, USA

ARTICLE INFO

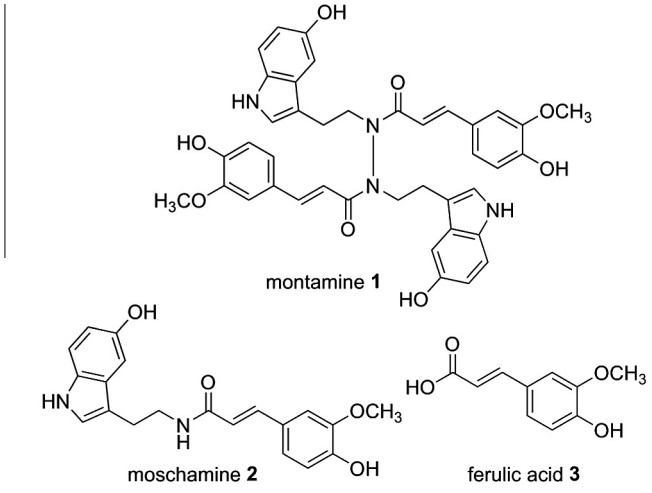
Article history:
Received 11 July 2013
Accepted 26 July 2013
Available online 2 August 2013

Keywords:
Montamine
Bidirectional synthesis
Alkylation
Fischer indole synthesis
Aryl ether demethylation

ABSTRACT

Reported herein is a bidirectional synthesis of symmetric *N*,*N*′-diacyl hydrazide compounds closely resembling the alkaloid natural product montamine. In the process, di-*tert*-butyl hydrazine-1,2-dicarboxylate was smoothly dialkylated with alkyl halides, then Boc deprotected and acylated with an acetate-protected acid chloride derived from ferulic acid. After acetate removal, simple montamine analogs were obtained in excellent overall yields. Fischer indole synthesis with 4-methoxyphenylhydrazine hydrochloride and dihydrofuran provided 5-methoxytryptophol, which was then elaborated to the 1,2-bis(5-methoxyindol-3-yl)hydrazide structure bearing the substitution pattern found in montamine.

Many plant species within the genus *Centaurea* have been used in traditional medicine for the treatment of various ailments.[1] *Centaurea montana*, also known as the mountain cornflower, is a plant native to Europe and Australia.[2] The seeds of *C. montana* contain a number of natural products[3–5] including montamine (**1**).[6] This natural product has a unique dimeric *N*,*N*′-diacyl hydrazide structure and displays cytotoxicity against CaCo-2 colon cancer cells (IC_{50} = 43.9 μM). Notably, the amide monomer, moschamine (**2**), is also produced by the plant with a reported cytotoxicity against CaCo-2 cells (IC_{50} = 81.0 μM). Moschamine appears to be derived from another common natural product, ferulic acid (**3**).[7] The production of **1** and **2** hints at a possible biosynthesis of **1** by an oxidative dimerization of **2**, though no such pathway has yet been reported. The near half potency of moschamine compared to montamine raises questions about the mode of cytotoxicity of both compounds. To address these questions, we have been pursuing a flexible synthesis of montamine and analogs to conduct a structure–activity relationship study.[8] We focused on a bidirectional synthesis starting from a hydrazine core.[9] While hydrazine appears to be an attractive starting compound for the elaboration of montamine analogs through symmetric dialkylation followed by diacylation, this is not a viable strategy because hydrazine is prone to nonselective alkylation.[10] Instead, we selected di-*tert*-butyl hydrazine-1,2-dicarboxylate (**4**) to force symmetric dialkylation.[11–15] We envisioned that subsequent removal of the BOC groups followed by diacylation would furnish montamine analogs (see Scheme 1).



We tested the feasibility of our route through the synthesis of a simple montamine analog in which butyl groups were added in the dialkylation process (Scheme 2). This process proceeded smoothly as previously reported,[15] furnishing **5** in 90% yield when NaH and 4 equiv of butyl bromide were used. (Yields were lower and the reaction was significantly slower when Cs_2CO_3 was used.) Next, we investigated conditions for the BOC deprotection and found the in situ generation of HCl through treatment with methanol and acetyl chloride[16] to be efficacious and convenient. The crude deprotected residue was immediately subjected to different acylation conditions. Disappointingly, coupling attempts with ferulic acid under several standard conditions did not cleanly afford the desired *N*,*N*′-diacyl hydrazide structure. We next turned to the use of the acetate-protected acid chloride (**6**)[17] derived from ferulic

* Corresponding author. Tel.: +1 508 767 7264; fax: +1 508 767 7241.
E-mail address: ecolbydavie@assumption.edu (E.A.C. Davie).

0040-4039/$ - see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tetlet.2013.07.134

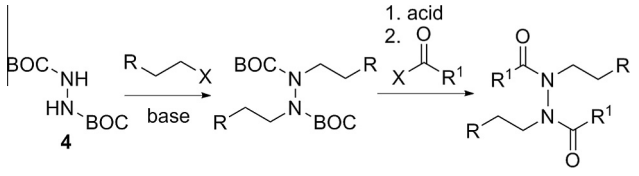
acid and found that diacylation was smooth as long as an excess of **6** was used (6 equiv were optimal). The acetate protecting groups were removed from the crude residue through refluxing with NaOMe in methanol,[18] providing a rotameric mixture of diacyl hydrazide **7** in 88% yield over the BOC removal, acylation, and acetate removal steps. Since these 3 steps represent six chemical transformations, the overall yield is particularly notable because it indicates that each individual reaction averaged >97% yield with only one purification needed.

Encouraged by the synthesis of **7**, we turned our attention to installation of the requisite (indolyl)ethyl group in place of a simple alkyl group. We were concerned about elimination complicating the dialkylation step because of the formation of a conjugated alkene. To investigate this potential competing process, we chose a simple model system using a phenyl group in place of the more complex indole moiety (Scheme 3). Indeed, the formation of styrene was observed in reaction mixtures by crude NMR analysis, but good yields of **8** were still obtained. Reactions conducted with Cs_2CO_3 in place of NaH were slower and lower in yield, although less styrene was formed. Elaboration of compound **8** to the corresponding montamine analog **9** was carried out in excellent yield over 3 steps.

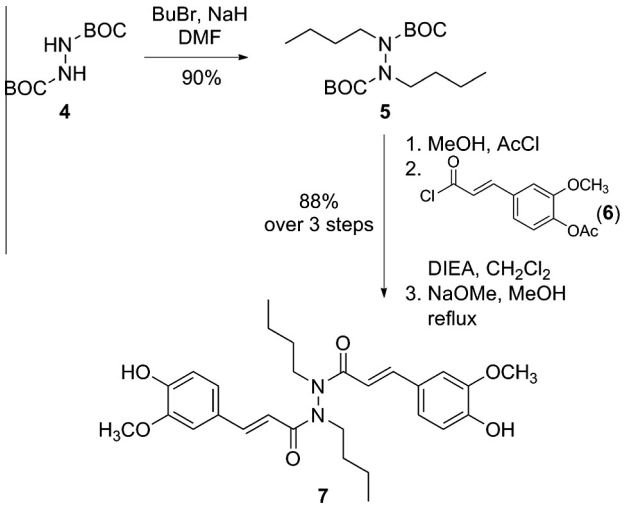
With the successful synthesis of diacyl hydrazide **9** containing (aryl)ethyl groups, we aimed to introduce the needed 2-(5-hydroxyindolyl)ethyl portion to complete the synthesis of montamine. While 5-hydroxytryptophol is an attractive starting material, its cost was prohibitive to our investigation. Instead, we synthesized 3-(2-hydroxyethyl)-5-methoxyindole (commonly known as 5-methoxytryptophol, **11**) via the Fischer indole synthesis with 4-methoxyphenylhydrazine hydrochloride (**10**) and 2,3-dihydrofuran (Scheme 4).[19,20] While the yield of this reaction was modest, it nevertheless provided an affordable, one-step route to an indole appropriately functionalized with an oxygen substituent at the 5-position and ethyl alcohol moiety at the 3-position. Alcohol **11** was subjected to tosylation conditions, affording ditosylate **12** in good yield.

With ditosylate **12** in hand, we tested its suitability as an electrophile in the dialkylation of di-*tert*-butyl hydrazine-1,2-dicarboxylate (**4**). When NaH was used as the base, a complex mixture of products was formed with strong indication of competing elimination. When the base was changed to Cs_2CO_3, the reaction proceeded smoothly, albeit slowly. After stirring for 36 h at room temperature, dialkylated product **13** was isolated in 81% yield as a mixture of rotamers. When allowed to stir for 5 days, a quantitative yield was obtained (Scheme 5).[21] Additionally, excess ditosylate was easily recovered in good yield and purity. Subjection of **13** to our standard sequence of conditions for BOC removal, acylation, and acetate removal was successful in introducing the feruloyl functionality while concomitantly removing the Ts protecting groups, furnishing advanced montamine analog **14** in 55% yield.

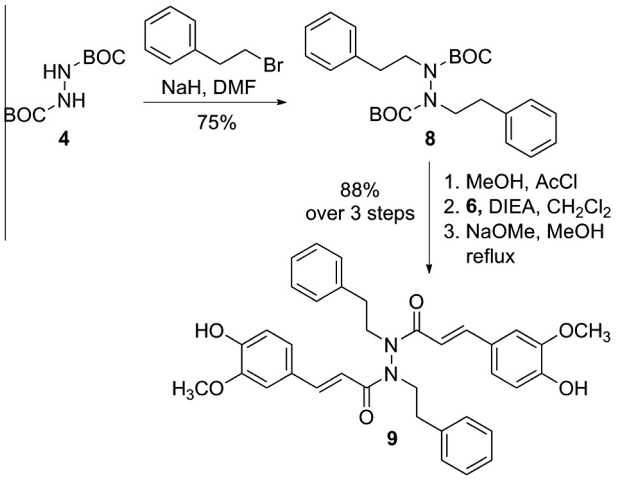
With the synthesis of montamine being our ultimate goal, we attempted to demethylate the indole aryl ethers after dialkylation to avoid selectivity issues with the feruloyl aryl methyl ethers. We expected that **13** would undergo demethylation[22,23] and BOC deprotection[24] upon exposure to BBr_3. Indeed, this reaction



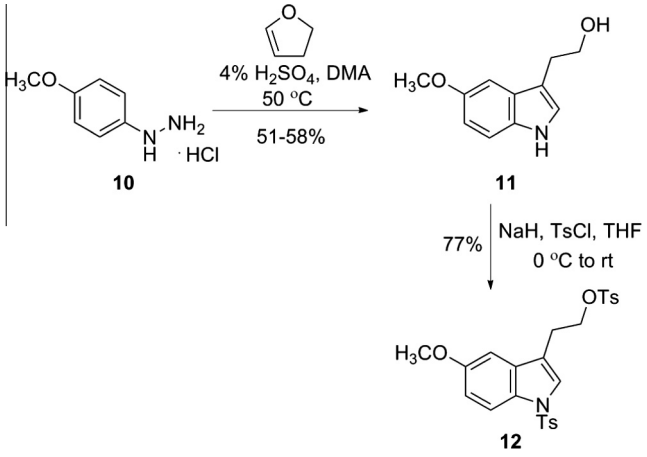
Scheme 1. Proposed bidirectional synthetic route.



Scheme 2. Proof-of-concept case.

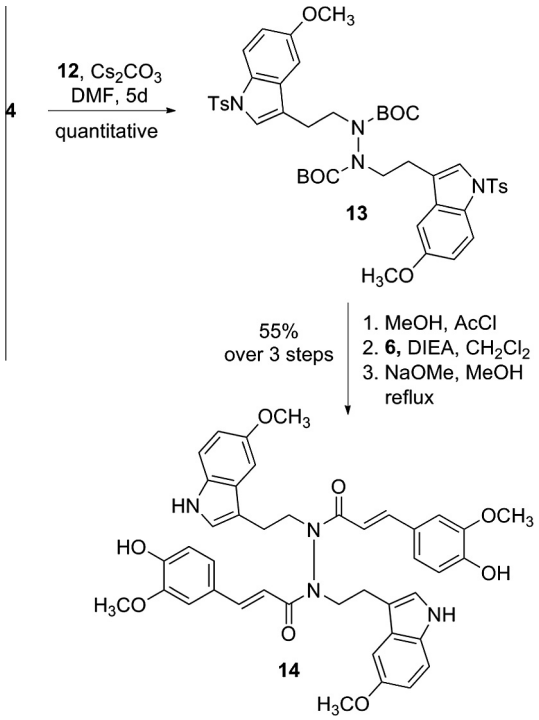


Scheme 3. Introduction of an (aryl)ethyl group.

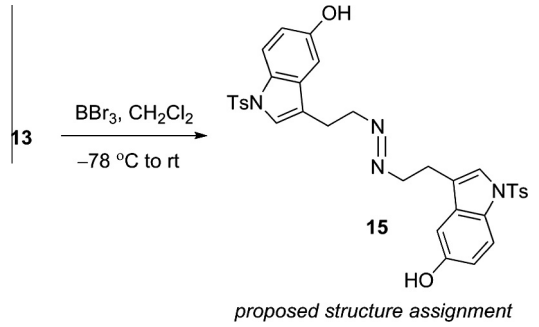


Scheme 4. Fischer indole synthesis with dihydrofuran.

produced one major product which lacked the signature methyl ether and BOC singlets in the ^{1}H NMR spectrum. However, upon analysis by LRMS, the expected mass was 2 units lower than expected, leading us to suspect that the N–N bond was also



Scheme 5. Synthesis of an advanced montamine analog.



Scheme 6. Demethylation attempt.

oxidized[25,26] producing the corresponding diazo compound **15** (Scheme 6). Further evidence supporting this structure assignment is the observation that the compound could not be acylated under our standard conditions. To circumvent this issue, we attempted to demethylate the indole before it was added to the hydrazine framework. Unfortunately, all efforts to demethylate 5-methoxytryptophol (**11**) have led to significant decomposition.

While the total synthesis of montamine remains elusive, we have developed a flexible, bidirectional route to symmetric *N*,*N*′-diacyl hydrazide compounds containing two feruloyl units, including a compound possessing two 2-(5-methoxyindol-3-yl)-ethyl portions that parallels the structure of montamine (**1**). Our process is efficient, providing significant quantities of these analogs for biological assays. Further investigations are focused on synthesizing 2-(5-oxyindol-3-yl)ethyl alcohols with protecting groups that are orthogonal to other conditions in our synthetic sequence and more labile than aryl methyl ethers.

Acknowledgments

Assumption College is acknowledged for support of this work. Acknowledgment is made to the donors of the American Chemical Society Petroleum Research Fund for partial support of this research (48347-GB1). High resolution mass spectrometry analysis was carried out at the University of Illinois on a Q-Tof Ultima mass spectrometer which was purchased in part with a grant from the National Science Foundation, Division of Biological Infrastructure (DBI-0100085). Thanks are extended to Xiaopeng Bai and Vera Bodmer (GlaxoSmithKline) for assistance with obtaining NMR data.

Supplementary data

Supplementary data (experimental procedures, NMR spectra (^{1}H and ^{13}C) and HRMS data for new compounds) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.07.134.

References and notes

1. Karamenderes, C.; Konyalioglu, S.; Khan, S.; Khan, I. A. *Phytother. Res.* **2007**, *21*, 488–491.
2. USDA, ARS, National Genetic Resources Program.Germplasm Resources Information Network-(GRIN) [Online Database]. National Germplasm Resources Laboratory, Beltsville, Maryland. URL: http://www.ars-grin.gov/cgi-bin/npgs/html/taxon.pl?401601 (accessed July 5, 2013).
3. Gonnet, J.-F. *Biochem. Syst. Ecol.* **1996**, *24*, 447–460.
4. Gonnet, J.-F. *Biochem. Syst. Ecol.* **1992**, *20*, 149–161.
5. Christensen, L. P.; Lam, J. *Phytochemistry* **1991**, *30*, 3289–3292.
6. Shoeb, M.; MacManus, S. M.; Jaspars, M.; Trevidu, J.; Nahar, L.; Kong-Thoo-Lin, P.; Sarker, S. D. *Tetrahedron* **2006**, *62*, 11172–11177.
7. Sarker, S. D.; Savchenko, T.; Whiting, P.; Sik, V.; Dinan, L. N. *Nat. Prod. Lett.* **1997**, *9*, 189–199.
8. Davie, E. A. C.; Dion, M. A.; Dugas, G. J.; St. Louis, J. M.; Lupien, L. E. *Abstracts of Papers of the American Chemical Society*, 240th Meeting of the American Chemical Society, Boston, MA, Aug 22–26, **2010**; American Chemical Society: Washington, DC, **2010**; 1057-ORGN.
9. A recent publication describes a similar approach and reports progress toward the synthesis of montamine: Blair, L. M.; Sperry, J. *Tetrahedron Lett.* **2013**, *54*, 1980–1982.
10. Bredihhin, A.; Mäeorg, U. *Tetrahedron* **2008**, *64*, 6788–6793.
11. Dowd, P.; Paik, Y. H. *Tetrahedron Lett.* **1986**, *27*, 2813–2816.
12. Wang, C.; Zhen, Z.; Zhao, J.; Dowd, P. *Synth. Commun.* **1999**, *29*, 631–643.
13. Boros, E. E.; Bouvier, F.; Randhawa, S.; Rabinowitz, M. H. *J. Heterocycl. Chem.* **2001**, *38*, 613–616.
14. Wilkinson, D. E.; Thomas, B. E.; Limburg, D. C.; Holmes, A.; Sauer, H.; Ross, D. T.; Soni, R.; Chen, Y.; Guo, H.; Howorth, P.; Valentine, H.; Spicer, D.; Fuller, M.; Steiner, J. P.; Hamilton, G. S.; Wu, Y.-Q. *Bioorg. Med. Chem.* **2003**, *11*, 4815–4825.
15. Rasmussen, L. K. *J. Org. Chem.* **2006**, *71*, 3627–3629.
16. Nudelman, A.; Bechor, Y.; Falb, E.; Fischer, B.; Wexler, B. A.; Nudelman, A. *Synth. Commun.* **1998**, *28*, 471–474.
17. Prepared as reported by: Hosoda, A.; Nomura, E.; Mizuno, K.; Taniguchi, H. *J. Org. Chem.* **2001**, *66*, 7199–7201.
18. *O*-Ac-feruloyl amides were reported to hydrolyze under these conditions: Nomura, E.; Kashiwada, A.; Hosoda, A.; Nakamura, K.; Morishita, H.; Tsuno, T.; Taniguchi, H. *Bioorg. Med. Chem.* **2003**, *11*, 3807–3813.
19. This method for 5-methoxytryptophol preparation is reported on the following website, but to the best of our knowledge does not appear in the peer-reviewed literature: http://www.erowid.org/archive/rhodium/chemistry/tryptophol.html.
20. A related Fischer indole synthesis of 5-substituted tryptophols using 2-ethoxytetrahydrofuran has been reported. The tryptophol products are converted to the corresponding *O*,*N*-ditosylates. Adachi, H.; Palaniappan, K. K.; Ivanov, A. A.; Bergman, N.; Gao, Z.-G.; Jacobson, K. A. *J. Med. Chem.* **2007**, *50*, 1810–1827.
21. The authors of Ref. 9 report that attempts to dialkylate **4** with an indolyl mesylate similar to **12** were unsuccessful.
22. Palmer, B. D.; Thompson, A. M.; Booth, R. J.; Dobrusin, E. M.; Kraker, A. J.; Lee, H. H.; Lunney, E. A.; Mitchell, L. H.; Ortwine, D. F.; Smaill, J. B.; Swan, L. M.; Denny, W. A. *J. Med. Chem.* **2006**, *49*, 4896–4911.
23. Revial, G.; Jabin, I.; Lim, S.; Pfau, M. *J. Org. Chem.* **2002**, *67*, 2252–2256.
24. Wuts, P. G. M.; Greene, T. W. *Greene's Protective Groups for Organic Synthesis*; John Wiley & Sons: Hoboken, New Jersey, 2007. 4th ed.; pp 725–735.
25. Oxidation of the N–N bond in hydrazine carboxylates to the corresponding diazenes is known to occur in the presence of Br_2: (a) Zeigler, F. E.; Wender, P. A. *J. Am. Chem. Soc.* **1971**, *93*, 4318–4319; (b) Zeigler, F. E.; Wender, P. A. *J. Org. Chem.* **1977**, *42*, 2001–2003.
26. For other known hydrazine oxidation methods, see this report and the references cited within: Drug, E.; Gozin, M. *J. Am. Chem. Soc.* **2007**, *129*, 13784–13785.