ORGANIC LETTERS

2013
Vol. 15, No. 7
1602–1605

Synthesis of Skeletally Diverse and Stereochemically Complex Library Templates Derived from Isosteviol and Steviol

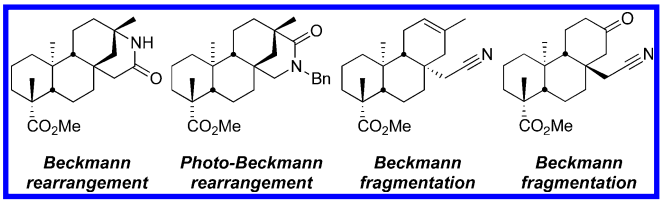
Oliver E. Hutt, Trinh L. Doan, and Gunda I. Georg*

Institute for Therapeutics Discovery and Development, Department of Medicinal Chemistry, College of Pharmacy, University of Minnesota, 717 Delaware Street SE, Minneapolis, Minnesota 55414, United States

georg@umn.edu

Received February 7, 2013

ABSTRACT



We have applied a diversity-oriented approach for the synthesis of skeletally diverse and stereochemically complex templates for small-molecule library production by performing Beckmann rearrangement and Beckmann fragmentation reactions on the bicyclo[3.2.1]octane rings of steviol and isosteviol, aglycones derived from the diterpene natural product stevioside. The optimization of these two reaction pathways is presented along with the successful application of a photo-Beckmann rearrangement. This work also led to the discovery of cyano-Prins-type and Thorpe–Ziegler-type cyclization reactions.

Major issues associated with the development of high-value information-rich small molecule libraries are achieving skeletal diversity, stereochemical complexity,[1] and mining areas of biologically relevant chemical space.[2] Natural products provide a solid platform for the discovery of biologically active small molecules.[3] It has been suggested that natural product-derived libraries should provide high screening hit rates because natural products have been evolutionarily molded by protein domains and are therefore likely to engage in interactions with conserved protein folds across protein families.[4] To date, the systematic exploration of many regions of natural product chemical space has not been possible due to the scarcity of accessible material. Steviol (**1**, Figure 1), however, is readily available from the natural sweetener stevioside (**5**, Scheme 1)[5] and an attractive template because stevioside (**5**) and its aglycones steviol (**1**) and isosteviol (**6**, Scheme 1) have shown diverse pharmacological activities.[6] Potentially, this scaffold could also provide access to templates representative of the large and diverse family of diterpenes derived from the methylerythritol 4-phosphate pathway[7] and subsequent metabolic processes. Representative diterpenes from this family include gibberellic acid derivative GA-13315 (**2**), oridonin (**3**), and cafestol (**4**) with antiangiogenic,[8] antitumor,[9] and neuroprotective properties,[10]

(1) (a) Burke, M. D.; Berger, E. M.; Schreiber, S. L. *Science* **2003**, *302*, 613. (b) Thomas, G. L.; Wyatt, E. E.; Spring, D. R. *Curr. Opin. Drug Discovery Dev.* **2006**, *9*, 700. (c) Mao, S.; Probst, D.; Werner, S.; Chen, J.; Xie, X.; Brummond, K. M. *J. Comb. Chem* **2008**, *10*, 235. (c) For a recent related approach see: Huigens, R. W., III; Morrison, K. C.; Hicklin, R. W.; Flood, T. A., Jr.; Richter, M. F.; Hergenrother, P. J. *Nat. Chem.* **2013**, *5*, 195.

(2) Feher, M.; Schmidt, J. M. *J. Chem. Inf. Comput. Sci.* **2003**, *43*, 218.

(3) Newman, D. J. *J. Med. Chem.* **2008**, *51*, 2589.

(4) Breinbauer, R.; Vetter, I. R.; Waldmann, H. *Angew. Chem., Int. Ed.* **2002**, *41*, 2878.

(5) Hanson, J. R.; De Oliveira, B. H. *Nat. Prod. Rep.* **1993**, *10*, 301.

(6) Brahmachari, G.; Mandal, L. C.; Roy, R.; Mondal, S.; Brahmachari, A. K. *Arch. Pharm. Chem. Life Sci.* **2011**, *1*, 5.

(7) Brandle, J. E.; Telmer, P. G. *Phytochemistry* **2007**, *68*, 1855.

(8) Zhang, Y.; Zhang, H.; Chen, J.; Zhao, H.; Zeng, X.; Zhang, H.; Qing, C. *Invest. New Drugs* **2012**, *30*, 8.

(9) Zhou, G. B.; Kang, H.; Wang, L.; Gao, L.; Liu, P.; Xie, J.; Zhang, F. X.; Weng, X. Q.; Shen, Z. X.; Chen, J.; Gu, L. J.; Yan, M.; Zhang, D. E.; Chen, S. J.; Wang, Z. Y.; Chen, Z. *Blood* **2007**, *109*, 3441.

(10) Trinh, K.; Andrews, L.; Krause, J.; Hanak, T.; Lee, D.; Gelb, M.; Pallanck, L. *J. Neurosci.* **2010**, *30*, 5525.

10.1021/ol400385w
Published on Web 03/26/2013

respectively (Figure 1). These compounds have attracted much attention from the synthetic organic chemistry community and therefore, a large amount of literature has been produced over the last eight decades pertaining to the synthesis[11] and structural modification of stevioside (**5**)[12] and structurally related diterpenes.[13]

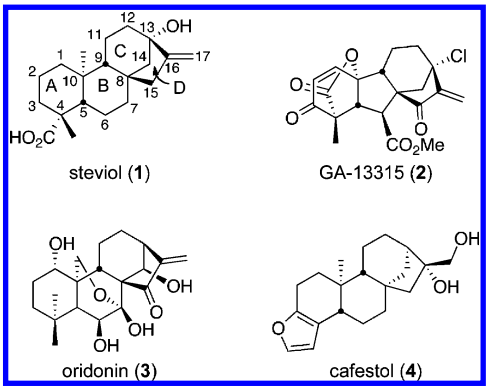


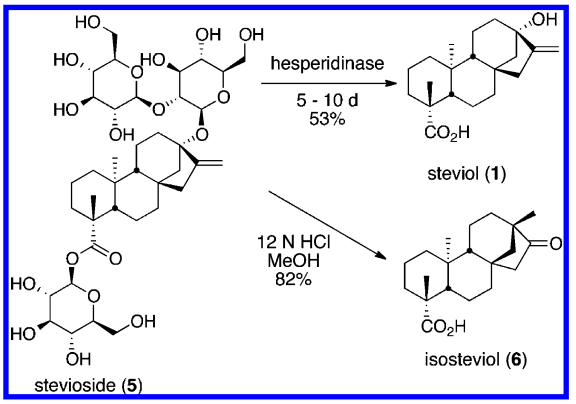
Figure 1. Representative examples of diterpenes.

We decided to employ the Beckmann rearrangement for ring expansion chemistry and the Beckmann fragmentation for ring cleavage reactions on the stevioside aglycones steviol (**1**) and isosteviol (**6**) for efficient generation of templates for library production.

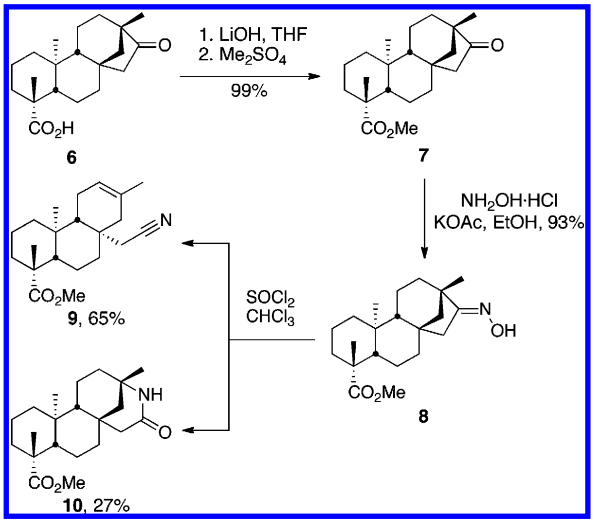
Steviol (**1**) was obtained through a well-precedented enzyme mediated hydrolysis of stevioside (**5**).[14,15] The D-ring isomer isosteviol (**6**) was obtained directly through a modification of existing methods and proceeds via a Wagner–Meerwein rearrangement (Scheme 1) of steviol (**1**).[16] Initially, we sought to access diverse heterocyclic intermediates through manipulation of the D-ring ketone of isosteviol (**6**, Scheme 2).

Although the Beckmann rearrangement has previously been reported[17] regarding an analogous substrate (the *N*-methyloxime), the lactam was sufficiently attractive

Scheme 1. Access to Steviol (**1**) and Isosteviol (**6**)



Scheme 2. Beckmann Fragmentation and Rearrangement



to warrant further investigation. Methylation of the carboxylic acid moiety of isosteviol (**6**) under standard conditions delivered methyl ester **7**. The ketone function of **7** was converted to the corresponding oxime **8** in 93% yield on treatment with hydroxylamine and potassium acetate. Reaction with thionyl chloride as reported[17] then delivered nitrile **9**, the corresponding Beckmann fragmentation product, in 65% yield and lactam **10** in 27% yield. The Beckmann fragmentation is well precedented[18] in systems with a quaternary α-carbon. This pathway significantly retarded the yield of lactam **10** if fresh thionyl chloride was not used. Use of fresh thionyl chloride provided nitrile **9** in 11% yield and lactam **10** in 55% yield. A more robust two-step procedure is outlined in Scheme 3. The conversion of the oxime hydroxyl group in **8** to the mesylate followed by treatment with acid in methanol exclusively led to the desired lactam **10** in 87% yield. It is of interest that this procedure appears to shut down the Beckmann fragmentation. We propose that this reaction proceeds via a tetrahedral

(11) (a) Cook, I. F.; Knox, J. R. *Tetrahedron Lett.* **1970**, 4091. (b) Mori, K.; Nakahara, Y.; Matsui, M. *Tetrahedron Lett.* **1970**, 2411. (c) Nakahara, Y.; Mori, K.; Matsui, M. *Agric. Biol. Chem.* **1971**, *35*, 918. (d) Mori, K.; Nakahara, Y.; Matsui, M. *Tetrahedron* **1972**, *28*, 3217. (e) Ziegler, F. E.; Kloek, J. A. *Tetrahedron* **1977**, *33*, 373. (f) Ogawa, T.; Nozaki, M.; Matsui, M. *Tetrahedron* **1980**, *36*, 2641.

(12) (a) Coates, R. M.; Bertram, E. F. *Tetrahedron Lett.* **1968**, 5145. (b) Coates, R. M.; Bertram, E. F. *J. Org. Chem.* **1971**, *36*, 2625. (c) Terauchi, T.; Asai, N.; Doko, T.; Taguchi, R.; Takenaka, O.; Sakurai, H.; Yonaga, M.; Kimura, T.; Kajiwara, A.; Niidome, T.; Kume, T.; Akaike, A.; Sugimoto, H. *Bioorg. Med. Chem.* **2007**, *15*, 7098.

(13) (a) Wang, F.-P.; Liang, X.-T. *Alkaloids Chem. Biol.* **2002**, *59*, 1. (b) Mander, L. N. *Nat. Prod. Rep.* **2003**, *20*, 49. (c) Hanson, J. R. *Nat. Prod. Rep.* **2007**, *24*, 1332.

(14) Stevioside can be obtained in kilogram quantities from several vendors.

(15) Pezzuto, J. M.; Coompadre, C. M.; Swanson, S. M.; Nanayakkara, N. P. D.; Kinghorn, A. D. *Proc. Natl. Acad. Sci. U.S.A.* **1985**, *82*, 2478.

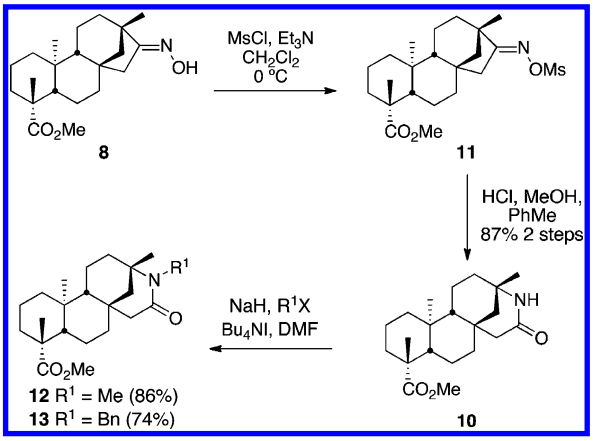
(16) Avent, A. G.; Hanson, J. R.; De Oliviera, B. H. *Phytochemistry* **1990**, *29*, 2712.

(17) Militsina, O. I.; Kovyljaeva, G. I.; Bakaleynik, G. A.; Strobykina, I. Y.; Kataev, V. E.; Alfonsov, V. A.; Musin, R. Z.; Beskrovny, D. V.; Litvinov, I. A. *Mendeleev Commun.* **2005**, 27.

(18) Gawley, R. E. *Org. React.* **1988**, *35*, 1.

intermediate in a similar fashion to that described by White et al., in which the less sterically crowded antistereoisomer favors the migration of the bridgehead carbon in lactam formation.[19] Lactam **10** was subsequently alkylated with methyl iodide and benzyl bromide to furnish compounds **12** and **13**, respectively. Despite being relatively hindered, this amide lends itself well to alkylation and should therefore prove useful in the development of small-molecule libraries of lactam derivatives.

Scheme 3. Optimized Beckmann Rearrangement of **11**

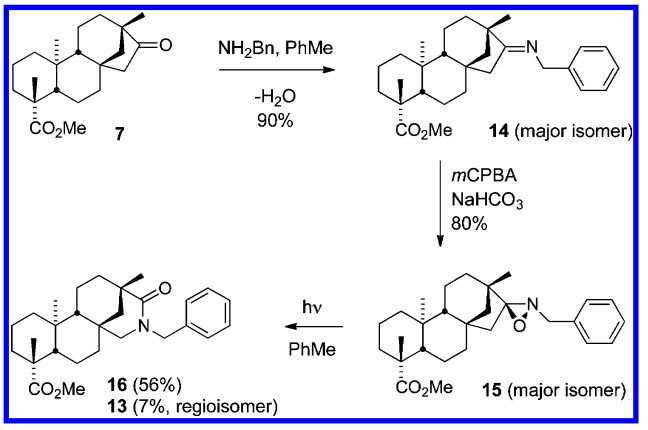


Next, we decided to access the regioisomeric lactam through the photolysis of an oxaziridine (Scheme 4).[20] Ketone **7** was converted to imines **14** through heating in the presence of benzylamine under dehydrating conditions.[21] The imines were formed in a 7:1 ratio (determined by ^{1}H NMR) in favor of the expected *E*-isomer vide infra. The imines **14** were subsequently epoxidized to furnish the oxaziridines **15** in 85% over two steps. Photolysis of the oxaziridines (254 nm, Hg lamp) then delivered lactam **16** in 56% yield as well as the regioisomer **13** in 7% yield. As with the Beckmann rearrangement, where the bond that migrates is that which is *anti* to the oxygen on nitrogen, the outcome of the photo-Beckmann is also stereoelectronically defined. As a general rule, the bond that migrates is the one *anti* to the lone pair on the nitrogen.[22] Therefore, the isolation of the regioisomeric lactam **16** confirms the assignment of the *E*-imine **14** as the major isomer.

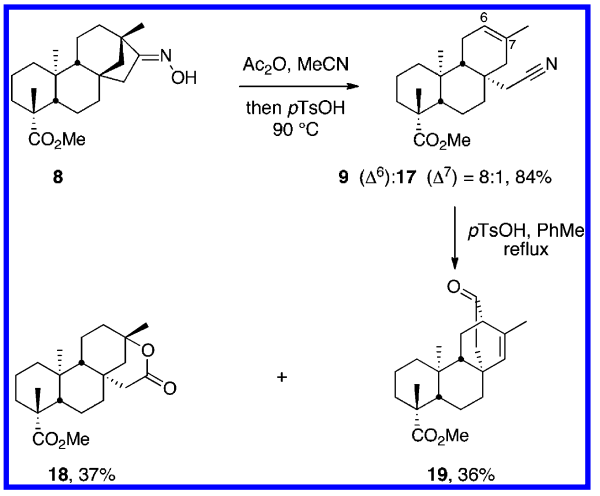
Having established synthetic routes to the *N*-alkylated isomeric lactams **13** and **16**, we recognized that nitrile **9** is also an attractive template for library design. However, in order to generate useful quantities of **9**, the Beckmann fragmentation pathway needed to be optimized (Scheme 5).

A similar fragmentation was recently reported by the Coates group for a closely related substrate employing TsCl in DMF as the reagent, but these reaction conditions

Scheme 4. Formation of Lactam **16**



Scheme 5. Optimized Beckmann Fragmentation of Isosteviol Oxime **8**



delivered a 2:1 mixture of the alkenes, which required a difficult separation.[23] Modification of reaction conditions through conversion of the oxime hydroxyl group in **8** to the corresponding acetate followed by treatment with *p*-TsOH in acetonitrile at 90 °C cleanly delivered nitriles **9** and **17** in 84% overall yield and in an 8:1 ratio of alkenes (determined by ^{1}H NMR). Through a single crystallization from dichloromethane and ethyl acetate, this mixture could be enriched to 20:1 in favor of the Δ^6-alkene. Interestingly, treating oxime **8** with Ac_2O, followed by reaction with *p*-TsOH in benzene as the solvent at reflux delivered a 2:0.2:1 ratio of nitriles **9**/**17** to lactam **10**. This suggests that the solvent plays an important role in the stabilization of the intermediates leading to either the lactam or nitrile. Attempts to drive the equilibrium to further favor the Δ^6-alkene (Scheme 5) unexpectedly led to the formation of bicyclo[2.2.2]octane **19** (36%) and lactone **18** (37%). The former most likely proceeds through a

(19) White, J. D.; Hrncliar, P.; Stappenbeck, F. *J. Org. Chem.* **1999**, *64*, 7871.
(20) Judd, W. R.; Katz, C. E.; Aube, J. *Sci. Synth.* **2005**, *21*, 133.
(21) Al'fonsov, V. A.; Andreeva, O. V.; Bakaleinik, G. A.; Beskrovnyi, D. V.; Gubaidullin, A. T.; Kataev, V. E.; Kovylyaeva, G. I.; Konovalov, A. I.; Korochkina, M. G.; Litvinov, I. A.; Militsina, O. I.; Strobykina, I. Y. *Russ. J. Gen. Chem.* **2003**, *73*, 1255.
(22) Aube, J. *Chem. Soc. Rev.* **1997**, *26*, 269.
(23) Roy, A.; Roberts, F. G.; Wilderman, P. R.; Zhou, K.; Peters, R. J.; Coates, R. M. *J. Am. Chem. Soc.* **2007**, *129*, 12453.

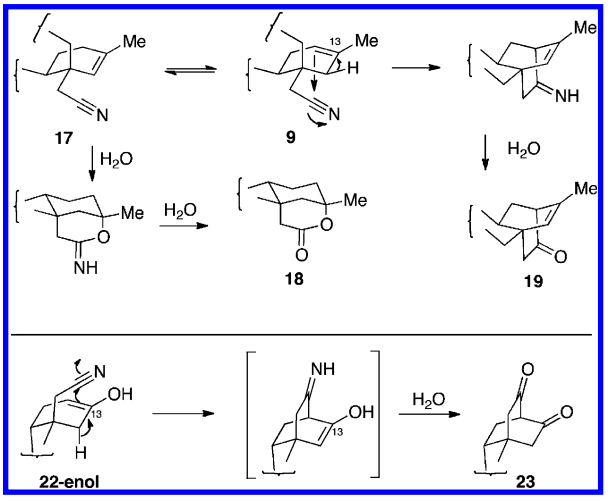


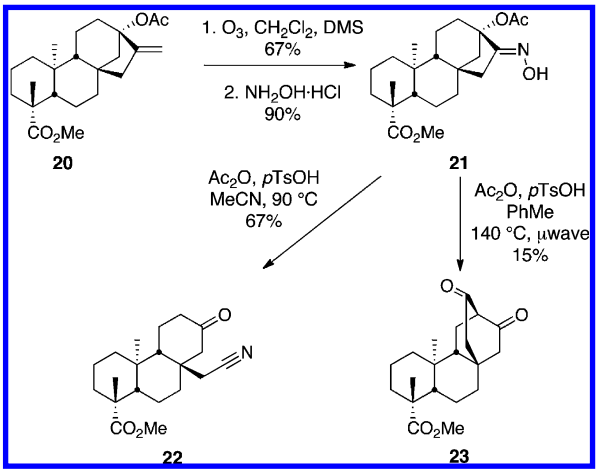
Figure 2. Proposed mechanisms for the formation of **18**, **19**, and **23**.

cyano-Prins-type cyclization, while the latter is derived through hydration of **17** followed by cyclization (Figure 2).

After having established the chemistry of the isosteviol system, we turned our attention to the steviol (**1**) scaffold since it seemed reasonable that a similar fragmentation would occur in this ring system (Scheme 6). Again, methylation of the acid function under standard conditions delivered the methyl ester (96%), which was subsequently treated with Ac_2O to provide acetate **20** (85%). The *exo*-methylene group in **20** was then ozonized to deliver the corresponding ketone in 67% yield. The ketone was converted to the oxime **21** in 90% yield and then treated with Ac_2O and *p*-TsOH in acetonitrile at 90 °C to deliver the expected nitrile **22** in 67% yield (Scheme 6). More vigorous heating in toluene initiated a Thorpe–Ziegler-type cyclization delivering the bicyclo[2.2.2]octane **23**.[24] The formation of **23** proceeds presumably in an analogous fashion to **19** (Figure 2).

In conclusion, we devised practical methods to access a number of diverse chemotypes, possessing high stereochemical complexity, and as single enantiomers from stevioside, which is readily available in kilogram quantities. We have shown a different approach toward the optimization of the Beckmann rearrangement of isosteviol to form lactam derivative **10** as the exclusive reaction product. Lactam **10** provides a classical point for diversification via *N*-alkylation. The regioisomeric lactams of type **16** can be obtained from ketone **7** as shown in Scheme 4 by reaction with diverse amines. Alternatively, a library can be prepared by removal of the *N*-benzyl group of **16**, followed by *N*-alkylation. Additionally, we demonstrated that the Beckmann fragmentation of isosteviol- and steviol-derived compounds form nitrile derivatives. The nitriles **9** and **22** will allow double functionalization via the ester and nitrile functional groups. The formation of **19** via a cyano-Prins-type cyclization and of **23** by a Thorpe–Ziegler-type reaction have not been previously reported. These types of reactions are underrepresented in the literature.

Scheme 6. Beckmann Fragmentation of Steviol Derivative **21**



Acknowledgment. We gratefully acknowledge financial support from the National Institutes of Health Grant No. GM081267 and the University of Minnesota through the Vince and McKnight Endowed Chairs.

Supporting Information Available. Experimental details and copies of ^1H and ^{13}C NMR spectra for compounds **6**–**10**, **12**, **13**, **15**, **16**, and **18**–**23**. This material is available free of charge via the Internet at http://pubs.acs.org

(24) Compound **23** has been prepared previously by a different route. Mori, K.; Nakahara, Y.; Matsui, M. *Tetrahedron* **1972**, *28*, 3217.

The authors declare no competing financial interest.