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A Highly Efficient Synthesis of Potent and Selective Butyrolactam Inhibitors of 11β-Hsd1†

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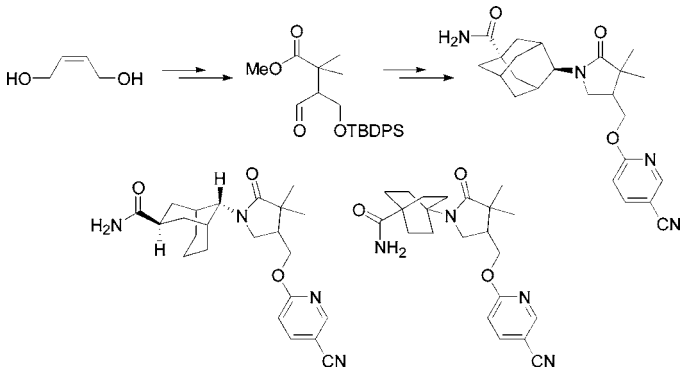
ABSTRACT



A convergent synthesis of structurally novel butyrolactam 11β-HSD1 inhibitors is described. The approach features an efficient Ireland–Claisen reaction to construct a highly substituted aldehyde building block which is converted to a lactam via a tandem reductive amination/cyclization sequence. The generality of the synthetic sequence is demonstrated during the preparation of two additional potent 11β-HSD1 inhibitors.

11β-Hydroxysteroid dehydrogenase 1 (11β-HSD1) converts the inactive glucocorticoid cortisone into the active hormone cortisol. Cortisol mediates a wide variety of physiological functions such as inflammatory and stress responses, growth and development, and gluconeogenesis.[1] A related enzyme, 11β-HSD2, catalyzes the reverse reaction which in tissues such as kidney protects the mineralocorticoid receptor from activation by cortisol. The current hypothesis is that tissue excess production of cortisol by 11β-HSD1 can lead to symptoms of metabolic syndrome, and selective inhibition of 11β-HSD1 over 11β-HSD2 may have potential for therapeutic intervention for diabetes.[2]

Our drug discovery program sought to identify potent and selective 11β-HSD1 inhibitors that possess desirable pharmacokinetic properties. This led us to a series of butyrolactams exemplified by **1**[3] (Figure 1). Lactam **1** is highly potent against human 11β-HSD1 and over 7600-fold in selectivity against 11β-HSD2. The biological evaluation and the struc-

† This paper is dedicated to professor Barry M. Trost on the occasion of his 65th birthday.

‡ Metabolic Disease Research.

§ Target and Lead Discovery Research.

|| Process Chemistry Research.

(1) For recent reviews, see: (a) Draper, N.; Stewart, P. M. *J. Endocrinol.* **2005**, *186*, 251. (b) Thieringer, R.; Hermanowski-Vosatka, A. *Expert Rev. Cardiovasc.* **2005**, *3*, 911. (c) Morton, N. M.; Paterson, J. M.; Masuzaki, H.; Holmes, M. C.; Staels, B.; Fievet, C.; Walker, B. R.; Flier, J. S.; Mullins, J. J.; Seckl, J. R. *Diabetes* **2004**, *53*, 931.

(2) (a) For a review on recent patents, see: Fotsch, C.; Askew, B. C.; Chen, J. *J. Expert Opin. Ther. Pat.* **2005**, *3*, 289. (b) For a general review on type 2 diabetes, see: Ross, S. A.; Gulve, E. A.; Wang, M. *Chem. Rev.* **2004**, *104*, 1255.

(3) All of the lactam compounds discussed in this paper are chiral racemic mixtures derived from the center denoted by * in Figure 1. Asymmetric synthesis of **1** will be published elsewhere.

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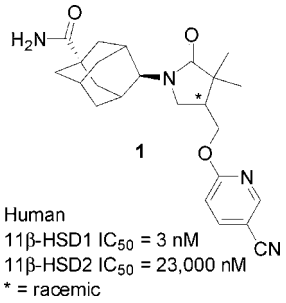
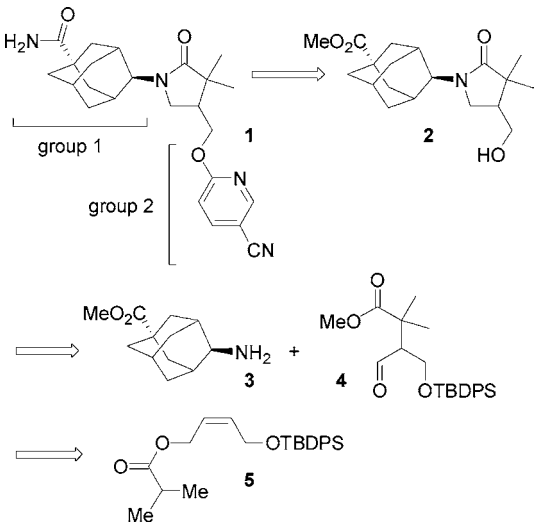


Figure 1. Lactam 11β-HSD1 inhibitor.

ture−activity relationships (SAR) of these lactams will be reported elsewhere.[4] We now report the development of an efficient and scalable route to these functionally dense and structurally unique lactams.

Lactam **1** features a highly substituted core with an α-*gem*-dimethyl quaternary center and a β-alkoxymethylene group. When we began, there was not a general synthetic route to this type of structure. We needed a route that would allow us to vary both group 1 and group 2 for SAR studies, as well as high convergency so that we could prepare these compounds on a multigram scale for in vivo studies. The design of our synthetic strategy is outlined in Scheme 1. We

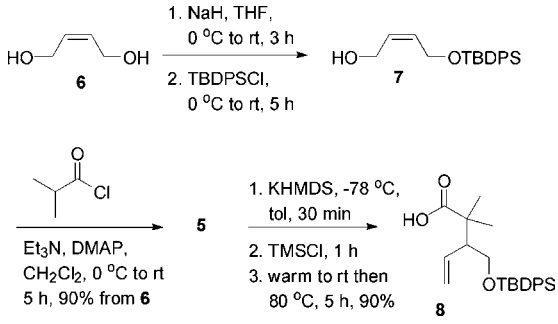
Scheme 1. Retrosynthesis of **1**



planned to make the heteroaryl ether bond near the end of the synthesis via a nucleophilic aromatic substitution reaction between alcohol **2** and a heteroaryl halide. The lactam core **2** was envisioned to be formed convergently through a sequential reductive amination/ring cyclization sequence[5] between amino ester **3**[6] and aldehyde **4**. The highly substituted aldehyde **4** could be built from an Ireland−Claisen rearrangement of ester **5**.[7]

The synthesis commenced with monosilylation[8] of commercially available diol **6**. Crude alcohol **7** was esterified with isobutyryl chloride to give ester **5** in 90% yield after purification (Scheme 2). We found the crucial Ireland−

Scheme 2. Synthesis of Acid **8**



Claisen rearrangement of **5** nontrivial since the formation of the silylenolether intermediate required the abstraction of a hindered α proton. Screening of common enolization reaction conditions using strong bases such as LDA, LiHMDS, or NaHMDS in THF gave either no desired product or <20% conversion along with decomposition products such as alcohol **7**. Soft enolization methods such as addition of TMSOTf to a CH_2Cl_2 solution of **5**, followed by the addition of *i*-Pr_2NEt, gave no observable silylenol either.[9] Ultimately, we achieved clean enolization with KHMDS in toluene. The reaction was optimal when a solution of ester **5** was added to a cold (−78 °C) suspension of KHMDS.[10] After the addition of TMSCl, the silyl enol ether was allowed to warm to room temperature followed by gentle heating (80 °C) to complete the rearrangement. After workup, acid **8** was isolated in 85−90% yield. This reaction has been scaled up to 50 g scale with reproducible yields.[11] Acid **8** was converted into the corresponding methyl ester using TMS-diazomethane

(4) (a) Yeh, V. S. C.; Kurukulasuriya, R.; Fung, S.; Monzon, K.; Chiou, W.; Wang, J.; Stolarik, D.; Imade, H.; Brune, M.; Jacobsen, P.; Link, J. T. *Bioorg. Med. Chem. Lett.* **2006**, submitted for publication. (b) The bridged bicyclic structures on the nitrogen of the lactam ring significantly contribute to potency and selectivity for 11β-HSD1. The current synthetic route crucially impacted our ability to determine the SAR of these inhibitors.

(5) Butyrolactam synthesis examples: (a) Duan, J. J.-W.; Chen, L.; Wasserman, Z. R.; Lu, Z.; Liu, R.-Q.; Convington, M. B.; Qian, M.; Hardman, K. D.; Magolda, R. L.; Newton, R. C.; Christ, D. D.; Wexler, R. R.; Decicco, C. P. *J.Med. Chem.* **2002**, *45*, 4954. (b) Duan, J. J.-W.; LU, Z.; Xue, C.-B.; He, X.; Seng, J. L.; Roderick, J. J.; Wasserman, Z. R.; Liu, R.-Q.; Convington, M. R.; Magolda, R. L.; Newton, R. C.; Trzaskos, J. M.; Decicco, C. P. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 2035. (c) Dolbeare, K.; Pontoriero, G. F.; Gupta, S. K.; Mishra, R. K.; Johnson, R. L. *J. Med. Chem.* **2003**, *46*, 727.

(6) Link, J. T.; Pliushchev, M. A.; Rohde, J. J.; Wodka, D.; Patel, J. R.; Shuai, Q. U.S. Patent 0245534, 2005.

(7) For reviews on Ireland−Claisen rearrangements, see: (a) Chai, Y.; Hong, S.-P.; Lindsay, H. A.; McFarland, C.; McIntosh, M. C. *Tetrahedron* **2002**, *58*, 2905. (b) Wipf, P. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon: Oxford, 1991; Vol. 5, p 827.

(8) a) Li, X.; Lantrip, D.; Fuchs, P. L. *J. Am. Chem. Soc.* **2003**, *125*, 14262. (b) McDougal, P. G.; Rico, J. G.; Oh, Y.-I.; Condon, B. D. *J. Org. Chem.* **1986**, *51*, 3388.

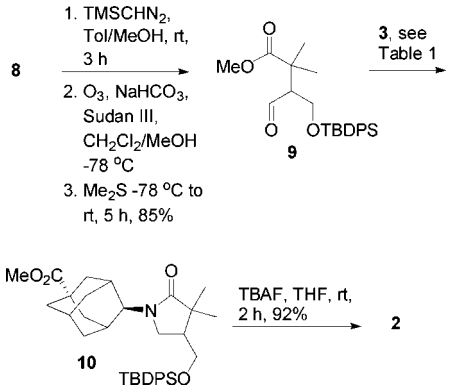
(9) Kobayashi, M.; Masumoto, K.; Nakai, E.; Nakai, T. *Tetrahedron Lett.* **1996**, *37*, 3005.

(10) Hong, S.-P.; Lindsay, H. A.; Yaramasu, T.; Zhang, X.; McIntosh, M. C. *J. Org. Chem.* **2002**, *67*, 2042.

(11) See the Supporting Information for experimental details.

(Scheme 3). The olefin was cleaved with O_3 to give a labile

Scheme 3. Ozonolysis and Lactam Formation



aldehyde **9**.[12] This reaction was at first problematic due to irreproducible yields on scales larger than 0.5 g. One of the side products isolated from the ozonolysis reaction mixture was lactone **11** (Figure 2). Ease of **11** formation is probably

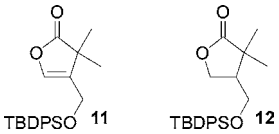


Figure 2. Lactone byproducts.

aided by the Thorp-Ingold effect[13] from the α-gem-dimethyl groups of aldehyde **9**. Upon optimization, we found that it was crucial to buffer the reaction mixture with $NaHCO_3$ and closely monitor the end point of ozonolysis with a dye indicator (Sudan III). Under optimized conditions, multigram amounts of aldehyde **9** were routinely obtained in >85% yield.

With aldehyde in hand, the stage was set for the lactam formation. Table 1 shows selected optimization results from the tandem reductive amination/cyclization reaction. Low yields were observed under standard reductive amination conditions where amine **3** and aldehyde **9** were stirred in the presence of a borohydride reagent (entries 1 and 2). Lactone **12** (Figure 2) was isolated as a major byproduct. The optimal conditions involved the preformation of an intermediate imine aided by molecular sieves followed by reduction with $NaHB(OAc)_3$. After filtration, concentration, and heating the residue in toluene, lactam **10** was obtained in >85% yield. The silyl group was then removed by TBAF giving alcohol **2** which served as a key intermediate for the SAR studies (Scheme 3).

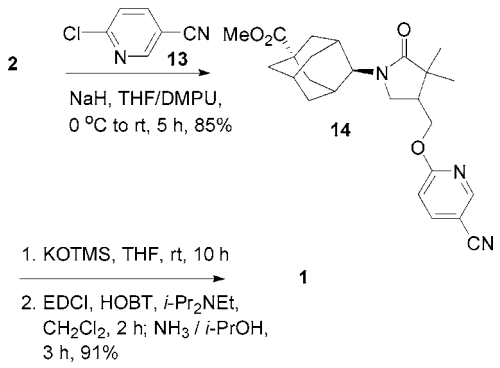
The completion of the synthesis of inhibitor **1** is depicted in Scheme 4. The nucleophilic heteroaromatic substitution

Table 1. Optimization of Lactam Formation (Scheme 3)

entry	conditions[a]	% yield of **10**[b]
1	(i) **3**, **9**, $NaCNBH_3$, AcOH, MeOH, rt, 12 h; (ii) reflux, 6 h	20
2	(i) **3**, **9**, $NaHB(OAc)_3$, THF, rt, 12 h; (ii) reflux, 6 h	35
3	(i) **3**, **9**, 4 Å MS, THF, 5 h; then add $NaBH_4$, rt, 12 h; (ii) reflux, 6 h	60
4	(i) **3**, **9**, 4 Å MS, THF, 5 h; then add $NaHB(OAc)_3$, rt, 12 h; (ii) toluene, 90 °C, 2 h	>85

[a] 1.1 equiv of **3** and 1 equiv of **9** were used. [b] Isolated yields.

Scheme 4. Synthesis of Lactam **1**



reaction of alcohol **2** and chloropyridine **13** was carried out by the addition of NaH to a solution of the two components in THF/DMPU to give ether **14** in 85% yield. Preformation of alkoxide of **2** led to dimerization of the starting material and lower isolated yield of the product **14**. Methyl ester **14** was then hydrolyzed by KOTMS, and the corresponding acid was converted into the final product **1** in good yield.

With a reliable route in hand, we were able to synthesize a variety of lactams with different *N*-substituents.[4] Here we demonstrate the synthesis of two lactams with unique functionalized bridged bicycles such as the bicyclo[3.3.1]-nonane amine **15** and the bicyclo[2.2.2]octane amine **16** shown in Figure 3.

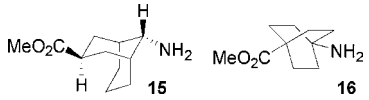
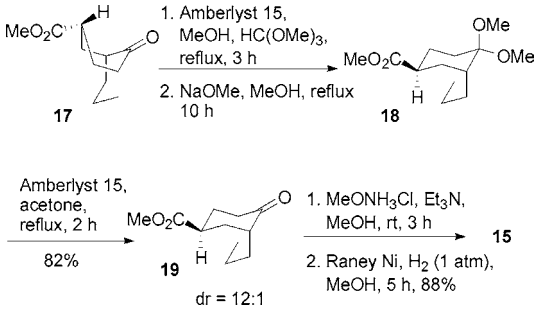


Figure 3. Functionalized bridged bicycle amines.

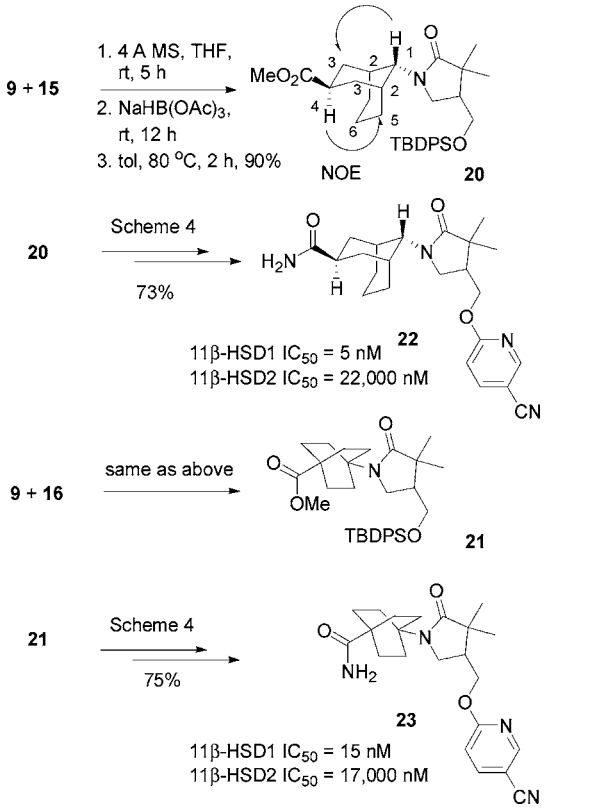
The bicyclo[2.2.2]octane amine **16** was synthesized following a literature procedure.[14] Scheme 5 shows the conver-

(12) Aldehyde **9** was usually prepared fresh before use.
(13) Beesley, R. M.; Ingold, C. K.; Thorpe, J. F. *J. Org. Chem.* **1915**, *107*, 1080.
(14) a) Reynolds, R. C.; Johnson, C. A.; Piper, J. R.; Sirotnak, F. M. *Eur. J. Med. Chem.* **2001**, *36*, 237. (b) Nuding, G.; Vogtle, F.; Danielmeier, K.; Stechhan, E. *Synthesis* **1996**, 71.

Scheme 5. Synthesis of Bicyclo[3.3.1]nonane Amine **15**



Scheme 6. Syntheses of Lactam Inhibitors **22** and **23**



sion of bicyclo[3.3.1]nonane ketone **17**[15] to amine **15**. Protection of ketone **17**, followed by NaOMe mediated epimerization and deprotection, gave the exo-ester **19** in good overall yield. Ketone **19** was condensed with methoxyamine to give an intermediate methoxyimine which was directly subjected to Raney Ni catalyzed hydrogenation to give the desired anti-amine **15** with high selectivity (>10:1) and yield. The stereochemistry of **15** was confirmed by NOE studies of a lactam derivative (see below).

The bicyclo[3.3.1]nonane amine **15** and aldehyde **9** were joined via the tandem reductive amination/lactam formation procedure that we developed (Scheme 6). The process worked reproducibly, giving a 90% yield of lactam **20**. NOE signals were observed between proton 1 and proton 3 (lactam **20**), as well as proton 4 and proton 5, hence confirming the stereochemistry of the substituents on the bicyclo[3.3.1]-nonane. Lactam **20** was converted into the final product following the reaction sequences shown in Scheme 4 giving inhibitor **22** in very good overall yield. Similarly, the bicyclo-[2.2.2]octane amine **16** was also carried forward to give lactam inhibitor **23** in similar overall yield. Similar to lactam **1**, both **22** and **23** are highly potent and selective inhibitors of 11β-HSD1.[4]

In conclusion, we have developed an efficient and scalable synthetic route to a series of highly substituted lactam 11β-HSD1 inhibitors. The synthesis features an Ireland−Claisen reaction to give an aldehyde with a α-gem-dimethyl quaternary center and a β-alkoxymethylene group. The aldehyde was then converted to the lactam core through a tandem reductive amination/cyclization reaction sequence. The current synthesis provided the flexibility of varying both ends of the lactam for SAR studies. These lactam inhibitors were instrumental in our study of 11β-HSD1 as a therapeutic target.

Acknowledgment. We thank David Wittern and the Structural Chemistry group at Abbott Laboratories for obtaining NMR spectra and for data analysis. We also thank Dr. Andrew Judd, J. T. Link, John Lynch, and Bruce Szczepankiewicz of Abbott Laboratories for helpful discussion.

Supporting Information Available: Detailed experimental procedures and ^{1}H and ^{13}C NMR spectra of the synthesized compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) Peters, J. A.; Van de Graaf, B.; Schuyl, J. W.; Wortel, T. H.; Van Bekkum, H. *Tetrahedron* **1976**, *32*, 2735.