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New Entry to Chiral Butenolide Synthons. Application to Expeditious Syntheses of (+)-Nephrosteranic Acid, (+)-*trans*-Whisky Lactone, and (+)-*trans*-Cognac Lactone

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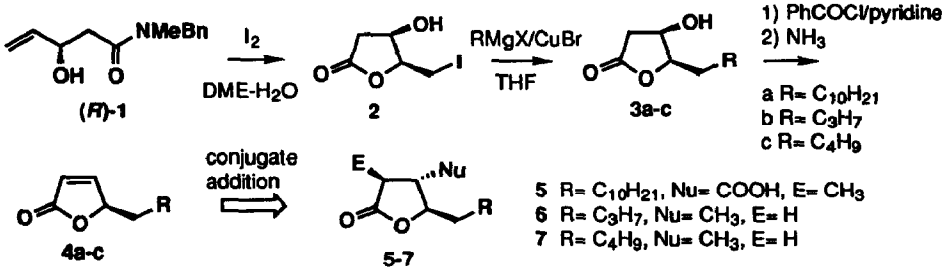
Abstract: A new entry to chiral butenolide synthons starting with iodolactonization of the readily available, homochiral *N*-benzyl-*N*-methyl-3-hydroxy-4-pentenamide (**1**) and its application to the syntheses of (+)-nephrosteranic acid (**5**), (+)-*trans*-whisky lactone (**6**), and (+)-*trans*-cognac lactone (**7**) are described.

Chiral butenolides have played a pivotal role in the construction of a variety of natural products.[1] Accordingly, the development of methods for their asymmetric synthesis continues to receive considerable attention.[2] Our interest in this field has focused on the synthetic utilization of electrophile-mediated heterocyclization,[3] as exemplified strongly in the stereoselective construction of oxygen- and nitrogen-heterocyles leading to natural products.[4] Herein we wish to communicate an attractive entry to a new chiral γ-butenolide synthon *via* stereoselective iodolactonization of homochiral *N*-benzyl-*N*-methyl-3-hydroxy-4-pentenamide **1** as shown in Scheme 1 and its application to expeditious syntheses of (+)-nephrosteranic acid (**5**), (+)-*trans*-whisky lactone (**6**), and (+)-*trans*-cognac lactone (**7**).



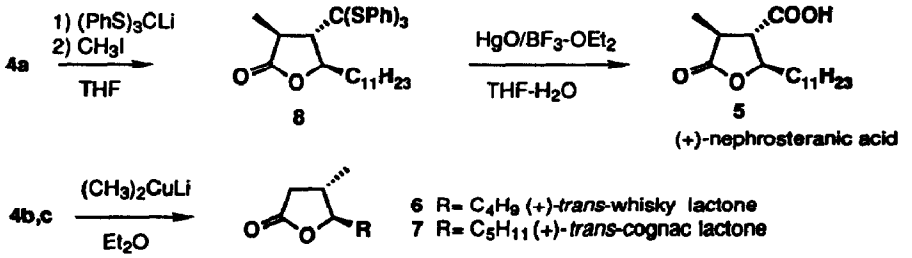
Scheme 1

Recent investigation in this laboratory has revealed that enzymatic resolution is effective for *N,N*-dialkyl-3-hydroxy-4-pentenamides while unsuccessful in resolution by the Katsuki-Sharpless asymmetric epoxidation.[5] Thus lipase-mediated resolution (immobilized Amano PS/vinyl acetate) of **1** gave the homochiral (*R*)-**1** (> 99% ee) in 44 % yield.[6] Iodolactonization of (*R*)-**1** provided the γ-lactone **2** in 54% yield with high (8:1= cis:trans) ratio due to direction by an allylic hydroxyl.[7] The cross coupling of the iodide cis-**2** with the Grignard-derived cupurates afforded **3a** (61%), **3b** (82%), and **3c** (83%), which were transformed into the butenolides **4a** (68%), **4b** (49%), and **4c** (50%), respectively, by benzoylation followed by elimination with ammonia in methanol.

With the requisite chiral butenolides **4** in hand, we turned our attention to the synthesis of biologically active compounds capitalizing on conjugate addition to the α,β-unsaturated lactone **4**.[8] At the beginning, we carried out the first asymmetric synthesis of **5**, isolated from *Nephromopsis endocrocea*.[9,10] The conjugate addition of a carboxyl anion equivalent, tris(phenylthio)methyllithium, to **4a** followed by quenching with methyl

iodide gave the adduct **8** (96% ee)[11] in 84% yield. In this way, the configuration at C4 may be used to control the absolute stereochemistry at C2 and C3 with excellent anti-stereoselectivity. Finally, **8** was converted to (+)-nephrosteranic acid (**5**)[12] {(mp 96-98 °C), lit.[9] (mp 95 °C)}, {$[\alpha]^{25}_D$ +27.2° ($CHCl_3$), (98% ee)[13] lit.[10] $[\alpha]_D$ +38.4° ($CHCl_3$)} by treatment with mercuric oxide in the presence of boron trifluoride-ether complex in 89% yield. Accordingly, the absolute configuration of **5** was unequivocally assigned to be *2S,3S,4R*.

In addition, the conjugate addition of dimethylcopperlithium to the butenolides **4b,c** in ether provided stereoselectively (+)-*trans*-whisky lactone (**6**)[12] {$[\alpha]^{25}_D$ +84.5° (MeOH), lit.[14] $[\alpha]^{25}_D$+79.5° (MeOH), 64% yield} and (+)-*trans*-cognac lactone (**7**) {$[\alpha]^{25}_D$ +82.2° (MeOH), lit.,[14] $[\alpha]^{25}_D$ +83.2° (MeOH), 72% yield}, respectively, which are key components of the flavors of whisky , wine, and cognac.[14]



Scheme 2

In summary, we have demonstrated a short, stereoselective synthesis of the chiral substituted γ-lactones **5-7** employing the conjugate addition to the butenolides **4a-c**, readily available *via* iodolactonization and olefination from homochiral **1**.

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Accordingly, the iodo lactone **2** should be served as the masked butenolide chiron **9** for the asymmetric synthesis of related biologically active compounds such as substituted γ-lactones [(+)-roccellaric acid,[15] (+)-protolichesterinic acid,[16] (+)-neodihydronurolic acid[10]] and pheromones,[17] and the results will be discussed in due course.[18]

References and Notes

1) a) Scott, J. W. In *Asymmetric Synthesis*, Morrisson, J. D.; Scott, J. W., Ed.; Academic Press, New York, 1984, vol 4, p1; b) Hanessian, S. *Pure & Appl. Chem.* **1993**, *65*, 1189.
2) Nagao, Y.; Dai, W.-N.; Ochiai, M.; Shiro, M, *J. Org. Chem.* **1989**, *54*, 5211 and references cited therein.
3) For a review see: Takahata, H. *Yakugaku Zasshi*, **1993**, *113*, 737.
4) Harding, K. E.; Timer, T. H. In *Comprehensive Organic Synthesis*, Trost, B. B., Ed.; Pergamon: Oxford, 1991; vol 4, p 363.
5) Takahata, H.; Uchida, Y.; Momose, T. *Tetrahedron: Asymmetry*, **1993**, *4*, 1041.
6) The acetyl pentenamide (49%) produced in this transesterification was converted to (*S*)-1 with 98% ee by ammonolysis (ref. 5).
7) a) Chamberlin, A. R.; Dezube, M.; Dussault, P.; McMills, M. C. *J. Am. Chem. Soc.* **1983**, *105*, 5819; b) Tamaru, Y.; Mizutani, M.; Furukawa, Y.; Kawamura, S.; Yoshida, Z.; Yanagi, K.; Minobe, M. *Ibid.* **1984**, *106*, 1079.
8) Perkmutter, P. In *Conjugate Addition Reactions in Organic Synthesis*, Baldwin, J. E., Ed.; Pergamon: Oxford, 1992; p283.
9) Asahina, Y.; Yanagita, M. *Ber. Dtsch. Chem. Ges.* **1937**, *70*, 227.
10) Huneck, S.; Schreiber, K.; Holfle, G.; Snatzke, G. *J. Hattori Bot. Lab.* **1979**, *45*, 1.
11) Determined by HPLC using Daicel chiral column AS.
12) Spectral data were identical with those reported.
13) Optical purity was determined by HPLC (Daicel chiral column AS) using benzyl ester of **5**. Surprisingly, our value of the optical rotation of **5** is lower than that reported in ref. 10. Accordingly, we are inquiring of Dr. Huneck about the high value for the natural **5**.
14) Ebata, T.; Matsumoto, K.; Yoshikoshi, H.; Koseki, K.; Kawakami, H.; Okano, K.; Matsushita, H. *Heterocycles*, **1993**, *36*, 1017 and references of other synthesis of **6** and **7** have been cited therein.
15) Huneck, S.; Follmann, G. *Z. Naturforsch. B* **1967**, *22*, 666.
16) Zopf, W. *liebigs Ann. Chem.* **1902**, *324*, 39.
17) Mori, K. In *The Total Synthesis of Natural Products*, ApSimon, J., Ed.; John Wiley: New York, 1992, vol 9, p1.

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