

Catalytic Enantioselective Synthesis of Naturally Occurring Butenolides via *Hetero-Allylic* Alkylation and Ring Closing Metathesis

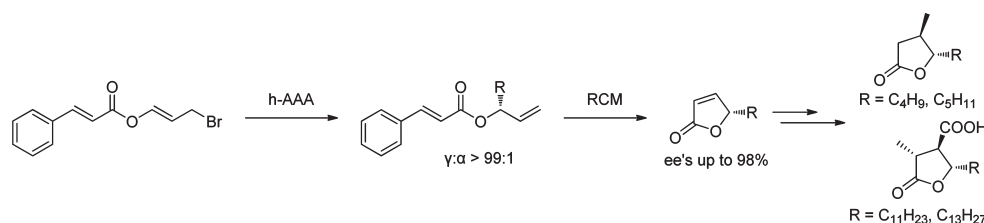
Bin Mao, Koen Geurts, Martín Fañanás-Mastral, Anthoni W. van Zijl, Stephen P. Fletcher, Adriaan J. Minnaard, and Ben L. Feringa*

Stratingh Institute for Chemistry, University of Groningen, Nijenborgh 4, 9747 AG Groningen, The Netherlands

b.l.feringa@rug.nl

Received December 10, 2010

ABSTRACT



An efficient catalytic asymmetric synthesis of chiral γ -butenolides was developed based on the *hetero*-allylic asymmetric alkylation (*h*-AAA) in combination with ring closing metathesis (RCM). The synthetic potential of the *h*-AAA-RCM protocol was illustrated with the facile synthesis of (–)-whiskey lactone, (–)-cognac lactone, (–)-nephrosteranic acid, and (–)-roccellaric acid.

The γ -butyrolactone skeleton is present in more than 13 000 natural products (Figure 1).¹ Due to the interesting biological activities such as antibiotic and antitumor properties, different asymmetric synthesis approaches to access γ -butyrolactones have been intensively investigated during the past decades.²

Brückner³ et al. described a route toward the synthesis of optically active butenolides through the Sharpless dihydroxylation⁴ of β,γ -unsaturated carboxylic esters.

Subsequently, iminium organocatalysis with siloxy furanones developed by the MacMillan group became one of the most powerful methods to obtain enantiomerically enriched γ -butyrolactones.⁵ Most recently, Trost and co-workers reported the first direct use of 2(5*H*)-furanone as a nucleophile in asymmetric Michael reactions employing a dinuclear zinc catalyst.⁶

Our group has been involved in asymmetric synthesis of butenolides over the past 20 years.⁷ A simple and inexpensive protocol to butenolides was developed based on the *D*-menthol derivatives of 5-hydroxy-2(5*H*) furanone.^{7a} Furthermore, an atom economic route was developed by using enantioselective acylation of 5-hydroxy-2(5*H*) furanone through lipase-catalyzed dynamic kinetic resolution

(1) For reviews, see: (a) Bandichhor, R.; Nosse, B.; Reiser, O. *Top. Curr. Chem.* **2005**, *243*, 43. (b) Kitson, R. R. A.; Millemaggi, A.; Taylor, R. J. K. *Angew. Chem., Int. Ed.* **2009**, *48*, 9426.

(2) For selective examples on the synthesis of optically active γ -butyrolactones, see: (a) Evans, D. A.; Kozłowski, M. C.; Murry, J. A.; Burgey, C. S.; Campos, K. R.; Connell, B. T.; Staples, R. J. *J. Am. Chem. Soc.* **1999**, *121*, 669. (b) Carswell, E. L.; Snapper, M. L.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2006**, *45*, 7230. (c) Ube, H.; Shimada, N.; Terada, M. *Angew. Chem., Int. Ed.* **2010**, *49*, 1858.

(3) (a) Harcken, C.; Brückner, R. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2750. (b) Braukmüller, S.; Brückner, R. *Eur. J. Org. Chem.* **2006**, 2110.

(4) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483.

(5) Brown, S. P.; Goodwin, N. C.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2003**, *125*, 1192.

(6) Trost, B. M.; Hitce, J. *J. Am. Chem. Soc.* **2009**, *131*, 4572.

(7) (a) Feringa, B. L.; de Lange, B.; de Jong, J. C. *J. Org. Chem.* **1989**, *54*, 2471. (b) van der Deen, H.; Cuiper, A. D.; Hof, R. P.; van Oeveren, A.; Feringa, B. L.; Kellogg, R. M. *J. Am. Chem. Soc.* **1996**, *118*, 3801.

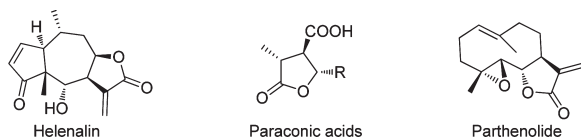
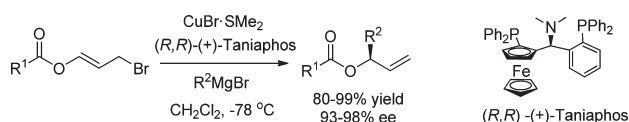


Figure 1. Natural products with γ -butyrolactone rings.

Scheme 1. Cu-Catalyzed *Hetero-Allylic Asymmetric Alkylation*^{8b}



(DKR), which offered the complete conversion of racemic furanone into the single enantiomer of γ -butyrolactone.^{7b}

Although a number of powerful methods have been described,² there is still a major incentive to develop efficient catalytic asymmetric protocols toward butenolides. Recently we reported an efficient catalyst system to accomplish highly enantioselective Cu-catalyzed allylic alkylations with Grignard reagents.^{8a} Novel prospects were offered by discovering that the transformation can also be performed with allylic esters through *hetero-allylic asymmetric alkylation* (*h*-AAA) with excellent enantiomeric control (Scheme 1).^{8b,9} As shown in Scheme 2, the reaction with cinnamyl ester **1** gives rise to compound **2** bearing two olefinic moieties. The olefinic substrates will directly lead to γ -butenolides by ring closing metathesis (RCM).^{10,11}

(8) (a) López, F.; van Zijl, A. W.; Minnaard, A. J.; Feringa, B. L. *Chem. Commun.* **2006**, 409. (b) Geurts, K.; Fletcher, S. P.; Feringa, B. L. *J. Am. Chem. Soc.* **2006**, *118*, 3801.

(9) For reviews, see: (a) Harutyunyan, S. R.; den Hartog, T.; Geurts, K.; Minnaard, A. J.; Feringa, B. L. *Chem. Rev.* **2008**, *108*, 2824. (b) Alexakis, A.; Bäckvall, J. E.; Krause, N.; Pamies, O.; Dieguez, M. *Chem. Rev.* **2008**, *108*, 2796. (c) Teichert, J. F.; Feringa, B. L. *Angew. Chem., Int. Ed.* **2010**, *49*, 2486.

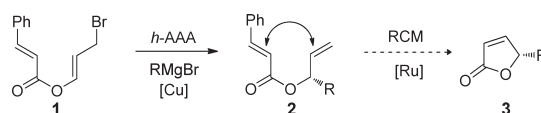
(10) For reviews, see: (a) Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18. (b) Monfette, S.; Fogg, D. E. *Chem. Rev.* **2009**, *109*, 3783.

(11) (a) Bassetti, M.; D'Annibale, A.; Fanfoni, A.; Minissi, F. *Org. Lett.* **2005**, *7*, 1805. (b) Fujii, M.; Fukumura, M.; Hori, Y.; Akita, H.; Nakamura, K.; Toriizuka, K.; Ida, Y. *Tetrahedron Lett.* **2006**, *17*, 2292.

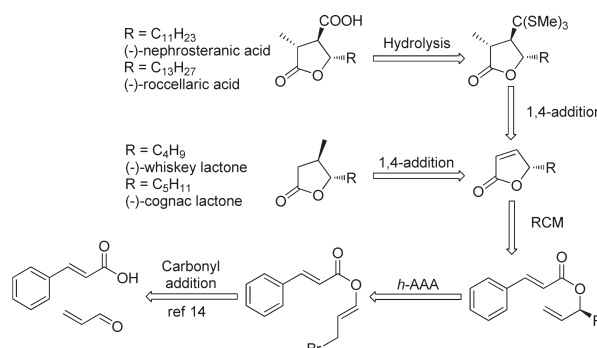
(12) (a) Takahata, H.; Uchida, Y.; Momose, T. *Tetrahedron Lett.* **1994**, *35*, 4123. (b) Takahata, H.; Uchida, Y.; Momose, T. *J. Org. Chem.* **1995**, *60*, 5628. (c) Ito, K.; Yoshitake, M.; Katsuki, T. *Tetrahedron* **1996**, *52*, 3905. (d) Nishikori, H.; Ito, K.; Katsuki, T. *Tetrahedron: Asymmetry* **1998**, *9*, 1165. (e) Tsuboi, S.; Sakamoto, J.; Yamashita, H.; Sakai, T.; Utaka, M. *J. Org. Chem.* **1998**, *63*, 1102.

(13) For selected examples of syntheses toward (–)-nephrosteranic acid and (–)-roccellaric acid, see: (a) Mulzer, J.; Salimi, N.; Hartl, H. *Tetrahedron: Asymmetry* **1993**, *4*, 457. (b) Bella, M.; Margarita, R.; Orlando, C.; Orsini, M.; Parlanti, L.; Piancatelli, G. *Tetrahedron Lett.* **2000**, *41*, 561. (c) Böhm, C.; Reiser, O. *Org. Lett.* **2001**, *3*, 1315. (d) Jacobi, P.; Herradura, P. *Can. J. Chem.* **2001**, *79*, 1727. (e) Sibi, M. P.; Liu, P.; Ji, J. G.; Hajra, S.; Chen, J. X. *J. Org. Chem.* **2002**, *67*, 1738. (f) Barros, M. T.; Maycock, C. D.; Ventura, M. R. *Org. Lett.* **2003**, *5*, 4097. (g) Chhor, R. B.; Nosse, B.; Sörgel, S.; Böhm, C.; Seitz, M.; Reiser, O. *Chem.—Eur. J.* **2003**, *9*, 260.

Scheme 2. Chiral γ -Butenolides via *h*-AAA Followed by RCM



Scheme 3. Retrosynthesis of (–)-Whiskey Lactone, (–)-Cognac Lactone, (–)-Nephrosteranic Acid, and (–)-Roccellaric Acid



Such a route could be a valuable alternative to current methods.^{1a}

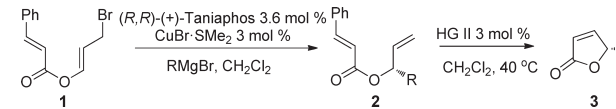
Whiskey and cognac lactones¹² are well-known perfume compounds with a distinct aroma, bearing the γ -butyrolactone ring as the main structure. (–)-Nephrosteranic acid and (–)-roccellaric acid¹³ are also naturally occurring γ -butyrolactones, containing a carboxylic acid group in the three position as their characteristic functionality. Despite extensive synthetic efforts toward their total synthesis using either chiral pool^{13a} or chiral auxiliaries,^{13c} there are limited reports on efficient catalytic enantioselective routes of these natural products.^{12,13}

Here we present a catalytic enantioselective synthesis of γ -butenolides via an *h*-AAA/RCM strategy. To further demonstrate the utility of this protocol, we report the concise total synthesis of (–)-whiskey lactone, (–)-cognac lactone, (–)-nephrosteranic acid, and (–)-roccellaric acid.

As shown in the retrosynthetic route (Scheme 3), starting from the inexpensive commercially available cinnamic acid and acrolein,¹⁴ the allylic ester is readily obtained. The key intermediate γ -butenolides could be prepared through the *h*-AAA-RCM protocol.¹⁵ Thus the desired natural products (–)-nephrosteranic acid and (–)-roccellaric acid would be possible to obtain after the conjugate addition

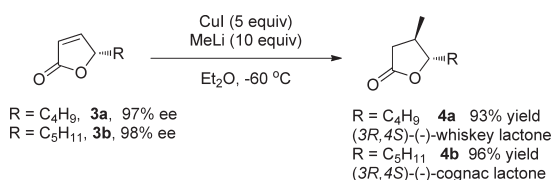
(14) (a) Lombardo, M.; Morganti, S.; Trombini, C. *J. Org. Chem.* **2003**, *68*, 997. (b) Lombardo, M.; Girotti, R.; Morganti, S.; Trombini, C. *Chem. Commun.* **2001**, 2310.

(15) For some consecutive AAA-RCM reactions, see: (a) Giacomina, F.; Riat, D.; Alexakis, A. *Org. Lett.* **2010**, *12*, 1156. (b) Teichert, J. F.; Zhang, S.; van Zijl, A. W.; Slaa, J. W.; Minnaard, A. J.; Feringa, B. L. *Org. Lett.* **2010**, *12*, 4658.

Table 1. *h*-AAA/RCM of Cinnamyl Substrate^a


entry	R	2	γ/α ^c	yield ^d (%)	3	time (h)	yield ^d (%)	ee ^{f,g} (%)
1	C ₄ H ₉	2a	>99:1	91	3a	24	83 (74) ^e	97
2	C ₅ H ₁₁	2b	>99:1	89	3b	24	82	98
3 ^b	C ₁₁ H ₂₃	2c	>99:1	84	3c	40	84	98
4 ^b	C ₁₃ H ₂₇	2d	>99:1	78	3d	40	82	97

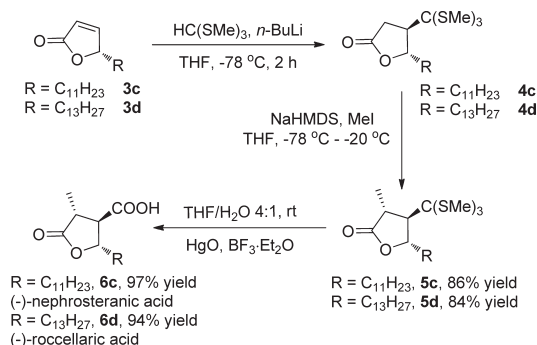
^a General conditions for *h*-AAA: 3 mol % of CuBr·SMe₂, 3.6 mol % of (*R,R*)-(+)-Taniaphos, 2 equiv of RMgBr in CH₂Cl₂ at −75 °C. ^b 3 equiv of RMgBr were employed at −55 °C. ^c Regioselectivity was determined by ¹H NMR spectroscopy. ^d Isolated yield. ^e Reaction was performed with a solution 4.6 mM of **2a**. ^f Ee was determined after converting compounds **2** to γ-butenolides **3**. ^g Determined by chiral HPLC analysis.

Scheme 4. Synthesis of (−)-Whiskey and (−)-Cognac Lactones

and subsequent enolate trapping to the corresponding γ-butenolides, followed by hydrolysis. The stereochemistry is anticipated to occur in a double *anti* fashion due to the directing influence of the alkyl substituent at γ-position. Analogously, the appropriate γ-butenolides could be converted to (−)-whiskey lactone and (−)-cognac lactone by straightforward 1,4-addition.

Our initial approach focused on the copper-catalyzed *h*-AAA reaction of cinnamyl substrate **1** with the corresponding Grignard reagents. Under the optimized conditions,^{8b} using 3 mol % CuBr·SMe₂ and 3.6 mol % (*R,R*)-(+)-Taniaphos, the desired products **2a** and **2b** were obtained in high yields with excellent regio- (>99:1) and enantioselectivities (97–98% ee) (Table 1, entries 1, 2). In accordance with our previous findings^{8b} no competing conjugate addition to the cinnamyl moiety was observed. To avoid the precipitation of the Grignard reagents, the temperature was increased to −55 °C when Grignard reagents with long alkyl chains were introduced (entries 3, 4).

As presented in Table 1, the regio- and enantioselectivities during formation of **2c** and **2d** were not affected by increasing the temperature. In addition, good yields were still obtained when the Grignard reagents bearing long alkyl chains (3 equiv) were added (entries 3, 4).

Scheme 5. Synthesis of (−)-Nephrosteranic Acid and (−)-Roccellaric Acid

With the isolated products **2** in hand, we turned our attention to the study of the ring closing metathesis (RCM) for diolefinic esters.¹¹ When a solution of **2a** (4.6 mM) was refluxed in CH₂Cl₂ with Hoveyda-Grubbs II catalyst (6 mol %), the desired furanone **3a** was obtained in 74% yield. However, a more concentrated solution of **2a** (0.2 M) allowed use of a lower catalyst loading (3 mol %), and provided compound **3a** in 83% yield with excellent enantiomeric excess (97% ee). Noteworthy, the reaction time was significantly reduced from 7 d to 24 h (entry 1). The same procedure was followed for substrates **2b–2d** (entries 2–4).

It should be pointed out that good isolated yields (up to 84%) and excellent ee (up to 98%) were found in all cases under the optimized conditions. The yield of the RCM step was still good despite the reaction time being extended for **2c** and **2d** with a longer alkyl substituent at the γ-position (entries 3, 4).

As shown in Scheme 4, chiral γ-butenolides **3a** and **3b** were used for the synthesis of (−)-whiskey and (−)-cognac lactone. The conjugate addition of dimethylcopper lithium (in situ formed from methyllithium and copper iodide in ether at −20 °C)^{12b} to butenolide **3a** provided **4a** in 93% yield with complete diastereoselectivity. The homologous lactone **4b** was prepared with 96% yield by performing the same reaction sequence. Their spectroscopic data and optical rotation were in agreement with those previously reported.¹²

Next we turned our attention to the synthesis of (−)-nephrosteranic acid and (−)-roccellaric acid (Scheme 5).¹³ We treated **3c** with lithiated tris(methylthio)methane at −78 °C,^{12b} followed by quenching the resulting enolate with methyl iodide (10 equiv) in the presence of HMPA.^{16a} The trisubstituted product **5c** was obtained in 46% yield, and the intermediate lactone **4c** was recovered in 42% yield.

Unfortunately the use of DMPU^{16b} instead of HMPA did not improve the double alkylation and a mixture of **4c** and trisubstituted γ-butyrolactone **5c** was obtained as well.

(16) (a) HMPA = Hexamethylphosphoramide. (b) DMPU = 1,3-Dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone.

Taking this into account, we considered the possibility of completing the formation of **5c** in two steps. After the addition of lithiated tris(methylthio)methane to **3c** was completed, the reaction was quenched with sat. aq. NH₄Cl solution. Then the crude product was treated with Na-HMDS¹⁷ and excess MeI at -78 °C. To our delight, the desired all *trans* product was obtained with 86% yield over two steps in a fully diastereoselective manner.

Efficient hydrolysis of **5c** afforded the final product (-)-nephrosteranic acid **6c** with excellent yield (97%). Analogously, γ -butenolide **3d** was converted to (-)-roccellaric acid **6d** in an overall yield of 79%. The *trans* configuration of the substituents at the γ -butyrolactones **6c** and **6d** was determined by comparison of the ¹H NMR spectroscopy data and optical rotation with those in literature.^{13c,d}

In summary, we have developed a novel enantioselective method toward the synthesis of chiral γ -butenolides based

on *h*-AAA in combination with an RCM strategy. The synthetic potential of this protocol is illustrated with the facile synthesis of (-)-whiskey and (-)-cognac lactone. Moreover, the biologically active γ -butyrolactones, (-)-nephrosteranic acid and (-)-roccellaric acid, were prepared efficiently with this catalytic enantioselective synthetic route.

Acknowledgment. Financial support from The Netherlands Organization for Scientific Research (NWO-CW) is acknowledged. B.M. thanks the China Scholarship Council for financial support (No. 2008618001). M.F.-M. thanks the Spanish Ministry of Science and Innovation (MICINN) for a postdoctoral fellowship. We thank M. Smith (GC and HPLC) and T. D. Tiemersma-Wegman (HRMS) for technical assistance.

Supporting Information Available. Detailed experimental procedures and full compound characterization data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

(17) (a) Schleth, F.; Vogler, T.; Harms, K.; Studer, A. *Chem.—Eur. J.* **2004**, *10*, 4171. (b) Schleth, F.; Studer, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 313.