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Asymmetric Synthesis of *trans*-3,4-Dialkyl-γ-butyrolactones via an Acyl-Claisen and Iodolactonization Route

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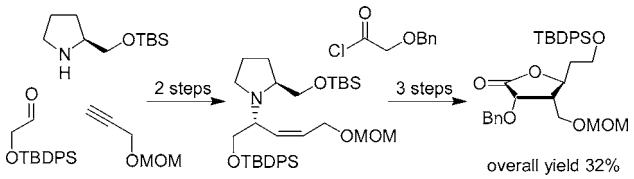
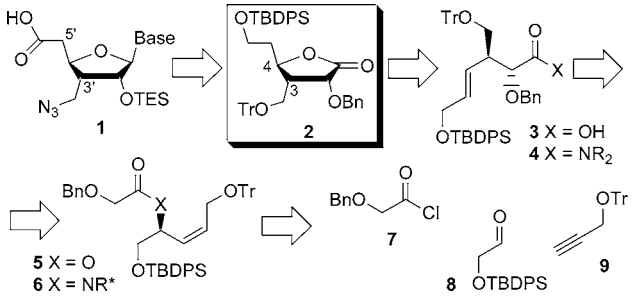
ABSTRACT



A new, efficient, and general asymmetric synthesis of enantiomerically pure *trans*-3,4-dialkyl-γ-lactones has been developed. The key steps are (1) copper-catalyzed three-component coupling of chiral amine, aldehyde, and alkyne, (2) acyl-Claisen rearrangement, and (3) iodolactonization. The products, chiral γ-lactones, are versatile synthetic intermediates and structural units of natural products and modified nucleosides.

Chiral *trans*-3,4-dialkyl-γ-butyrolactones are common structural units of natural products[1] and versatile intermediates in their total syntheses.[2,3] Despite the many approaches available for preparation of γ-lactones, stereoselective synthesis of highly substituted derivatives is still challenging. Our laboratory[4,5] and others[3] have used trisubstituted γ-butyrolactones bearing a 2-hydroxyl function (as exemplified by **2** in Scheme 1) to prepare C-branched nucleoside analogues. Similar intermediates have also been used in the total syntheses of rhizoxin D[2b] and bafilomycin A_1.[2c]

Scheme 1. Retrosynthetic Analysis of 3′,5′-C-Branched Nucleosides via the γ-Lactone Intermediate **2**



Traditional routes to γ-lactones having multiple hydroxyl groups (e.g., **2**) recognize their similarity with carbohydrates, which are readily available chiral pool starting materials. The advantages are that the carbon skeletons and the stereochemical relationships are in many cases already set in the starting carbohydrates or can be easily adjusted. However, carbohydrate routes are frequently lengthy and labor intensive because the multifunctional and sensitive intermediates

(1) For selected recent examples, see: (a) Avenaciolide: Aggarwal, V. K.; Davies, P. W.; Schmidt, A. T. *Chem. Commun.* **2004**, 1232−1233. (b) Nephrosteranic acid: Schleth, F.; Studer, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 313−315. (c) Paraconic acids: Barros, M. T.; Maycock, C. D.; Ventura, M. R. *Org. Lett.* **2003**, *5*, 4097−4099. (d) Sesquiterpenes: Nosse, B.; Chhor, R. B.; Jeong, W. B.; Boehm, C.; Reiser, O. *Org. Lett.* **2003**, *5*, 941−944.

(2) For recent examples, see: (a) Hale, K. J.; Dimopoulos, P.; Cheung, M. L. F.; Frigerio, M.; Steed, J. W.; Levett, P. C. *Org. Lett.* **2002**, *4*, 897−900. (b) White, J. D.; Blakemore, P. R.; Green, N. J.; Hauser, E. B.; Holoboski, M. A.; Keown, L. E.; Kolz, C. S. N.; Phillips, B. W. *J. Org. Chem.* **2002**, *67*, 7750−7760. (c) Hanessian, S.; Ma, J.; Wang, W. *J. Am. Chem. Soc.* **2001**, *123*, 10200−10206. (d) Peng, Z. H.; Woerpel, K. A. *Org. Lett.* **2001**, *3*, 675−678. (e) Refs 1b−d.

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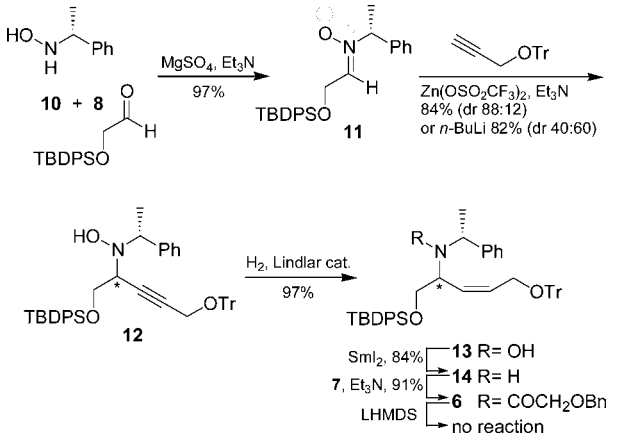
require extensive protecting group manipulations. For example, the synthesis of L-oxetanocin by Gumina and Chu required 10 steps for preparation of an intermediate similar to **2** in 36% yield starting from L-xylose.[3] Asymmetric syntheses that start from small organic molecules are potentially shorter and more efficient routes to highly substituted 2-hydroxy-γ-lactones.[4−6]

Recently, we reported[4] a total synthesis of 3′,5′-C-branched uridine **1** (Base = uracyl, TES = triethylsilyl, TBDPS = *tert*-butyldiphenylsilyl, Tr = trityl) (Scheme 1), which we are using as a monomer for preparation of amide-linked RNA analogues.[7] In our synthesis, we prepared γ-butyrolactone **2** from small achiral molecules (**7**−**9**) in only six steps and 29% yield using Ireland−Claisen rearrangement of **5** followed by iodolactonization of **3** as the key steps (Scheme 1). Although the total synthesis of **2** was shorter than analogous routes from carbohydrates,[4] several problems remained unsolved. First, the asymmetric propynylation[8] of aldehyde **8** with propargyl ether **9**, which we used as the first step to establish the absolute stereochemistry, gave a modest yield (50%) and enantioselectivity (ee 92%) with our substrates. The enantioselectivity was a particular concern because multiple couplings of azido acids **1** during the synthesis of amide-linked RNA would create complex mixtures of diastereomeric oligoamides. Second, the iodolactonization of carboxylic acid **3** was not stereoselective, and acceptable yields were obtained only after separation and recycling of the undesired 3,4-cis diastereomer, thus making the procedure laborious.

On the other hand, iodolactonization of amide **4** (Scheme 1) was expected, on the basis of our previous work,[5] to give respectable stereoselectivity.[9] Therefore, we hypothesized that an aza-Claisen rearrangement of **6** followed by iodolactonization of **4** would constitute a more efficient and general route to *trans*-3,4-dialkyl-γ-butyrolactones, including the desired intermediate **2**. Moreover, we envisioned that a chiral auxiliary (R*) bound to nitrogen in **6** or earlier intermediates could ensure high stereochemical purity of **1**, because the diastereomeric intermediates could be separated by conventional means. In this communication, we report the experimental realization of this design that resulted in a novel synthesis of *trans*-3,4-dialkyl-γ-butyrolactones from chiral propargylamines via an acyl-Claisen and iodolactonization route.

Initially, we attempted to access amide **4** via the aza-Claisen rearrangement[10] of allylic amide **6**. Synthesis of **6** (Scheme 2) started with the condensation of the known aldehyde **8**[11] with chiral hydroxylamine **10**[12] to give the nitrone **11**.[13]

Scheme 2. Aza-Claisen Route to *trans*-3,4-Dialkyl-γ-lactones



Addition of the trityl propargyl ether **9** to nitrone **11** under conditions developed by Carreira and co-workers[8b,14] resulted in the formation of two diastereomers in a ratio of 88:12. Interestingly, deprotonation of the alkyne with *n*-butyllithium reversed the diastereomeric ratio, but the stereoselectivity under these conditions was low (Scheme 2). At this point, we decided to probe the feasibility of the aza-Claisen rearrangement without determining the absolute stereochemistry at the newly established chiral center in **12**. If the planned syntheses were successful, the required absolute stereochemistry of the final product could be ensured by choosing the correct enantiomer of **10**.

Thus, both diastereomers of **12** were separated by silica gel column chromatography and separately converted into (*Z*)-alkenes **13** using Lindlar reduction. The anti relationship of the 2-OH and 3-alkyl substituents in **4** required the (*Z*)-configuration in **13**. The N−OH group was replaced by the benzyloxy acetyl function in a two-step sequence of N−O cleavage[15] and standard acylation with **7**. In contrast to our

(6) For selected recent examples, see: (a) Evans, D. A.; Wu, J.; Masse, C. E.; MacMillan, D. W. C. *Org. Lett.* **2002**, *4*, 3379−3382. (b) Chen, Y.; Eltepu, L.; Wentworth, P., Jr. *Tetrahedron Lett.* **2004**, *45*, 8285−8288. For earlier precedents similar to our approach, see: Okamura, H.; Kuroda, S.; Tomita, K.; Ikegami, S.; Sugimoto, Y.; Sakaguchi, S.; Katsuki, T.; Yamaguchi, M. *Tetrahedron Lett.* **1991**, *32*, 5137−5140. Okamura, H.; Kuroda, S.; Ikegami, S.; Tomita, K.; Sugimoto, Y.; Sakaguchi, S.; Ito, Y.; Katsuki, T.; Yamaguchi, M. *Tetrahedron* **1993**, *49*, 10531−10554. Konno, T.; Kitazume, T. *Tetrahedron: Asymmetry* **1997**, *8*, 223−230.

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(9) For similar precedents, see: Masaki, Y.; Arasaki, H.; Itoh, A. *Tetrahedron Lett.* **1999**, *40*, 4829−4832. Ha, H. J.; Lee, S. Y.; Park, Y. S. *Synth. Commun.* **2000**, *30*, 3645−3650. For recent reviews, see: Ranganathan, S.; Muraleedharan, K. M.; Vaish, N. K.; Jayaraman, N. *Tetrahedron* **2004**, *60*, 5273−5308. Robin, S.; Rousseau, G. *Tetrahedron* **1998**, *54*, 13681−13736.

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(13) Keirs, D.; Moffat, D.; Overton, K.; Tomanek, R. *J. Chem. Soc., Perkin Trans. 1* **1991**, 1041−1051.

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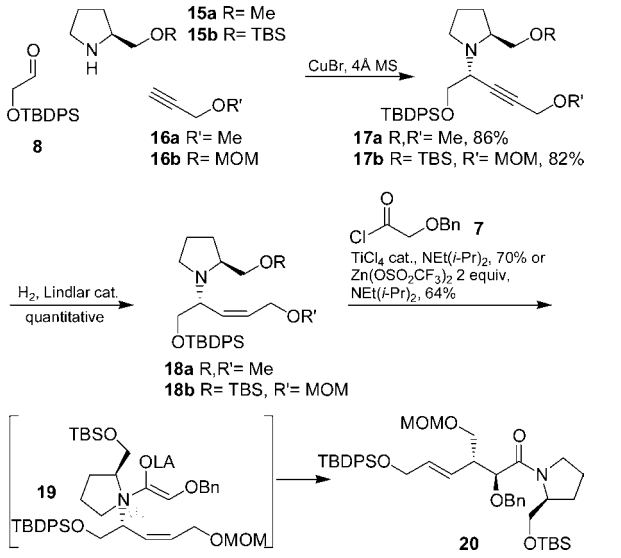
previous success with the Ireland−Claisen rearrangement, no attempts to engage either diastereomer of **6** into the aza-Claisen rearrangement gave the desired amide **4**. The lack of reactivity cannot be due to a mismatched stereochemical relationship of the *N*-α-methylbenzyl auxiliary and the allylic chiral center because neither diastereomer of **6** rearranged.[16] In general, the thermal aza-Claisen rearrangement requires higher temperatures and more reactive substrates than the Ireland−Claisen variant.[10] Although successful aza-Claisen rearrangements of (*E*)-allylic amides similar to **6** have been reported,[16,17] it is conceivable that the (*Z*)-configuration of the double bond and the bulky trityl protecting group prevented the rearrangement of **6**.[18]

We therefore explored alternative synthetic routes using an acyl-Claisen rearrangement[19] of (*Z*)-allylic amines **18a**,**b** having smaller protecting groups instead of the trityl group (Scheme 3). The acyl-Claisen is a charge-accelerated and

Scheme 3. Acyl-Claisen Route to *trans*-3,4-Dialkyl-γ-lactones



Lewis acid-promoted version of the aza-Claisen rearrangement that belongs to a larger group of zwitterionic [3,3]-sigmatropic rearrangements known under the names of ketene or Belluš−Claisen rearrangements.[10b,20] Mechanistically, the acyl-Claisen is believed to proceed through a charged intermediate **19** and a six-center cyclic transition state (Scheme 3).

The synthesis of **18a** started with a copper-catalyzed asymmetric three-component coupling of aldehyde **8**, amine **15a**, and methyl propargyl ether **16a** according to procedures developed by Knochel and co-workers.[21] The reaction gave a separable mixture of diastereomers (95:5) from which the desired propargylamine **17a** was isolated in 86% yield. The absolute stereochemistry at the newly formed center was assigned on the basis of the literature precedent.[21a] Lindlar reduction quantitatively converted **17a** into the required (*Z*)-allylamine **18a**.

Our initial attempts to induce the acyl-Claisen rearrangement of **18a** met with limited success. NMR analysis suggested that the reaction was incomplete and gave complex mixtures under a variety of conditions.[22] Next, we probed a slightly modified chiral amine **18b** that had *O*-*tert*-butyldimethylsilyl (TBS) and *O*-methoxymethyl (MOM) groups instead of methyl ethers. This modification was chosen with the reasoning that the low reactivity of **18a** might arise from an unfavorable conformation involving coordination of the Lewis basic methyl ether of the auxiliary with the Lewis acid promoter. In the event, substitution of methyl by TBS did improve the outcome of the acyl-Claisen rearrangement.

Propargylamine **17b** was prepared using the same three-component coupling as an 88:12 mixture of diastereomers from which pure **17b** was isolated in 82% yield and converted into **18b** using Lindlar reduction. Exposure of **18b** to MacMillan's conditions ($TiCl_4$ catalyst, $NEt(i\text{-}Pr)_2$, **7**) resulted in 75% conversion and gave the desired unsaturated amide **20** in 70% yield (based on recovered **18b**). Alternatively, the use of $Zn(OSO_2CF_3)_2$ as a Lewis acid resulted in complete consumption of **18b** and 64% yield of **20**. Several other Lewis acid/base combinations[22] were briefly investigated but gave either no reaction ($Me_3SiOSO_2CF_3$ and $Yb(OSO_2CF_3)_3$), incomplete conversion ($SnCl_4$), or complex mixtures ($AlMe_3$ and $Ti(Oi\text{-}Pr)_4$). Although further optimization of the chiral auxiliary and rearrangement conditions is clearly desirable and currently in progress in our laboratory, the preliminary results allowed us to proceed to the next iodolactonization step.

Exposure of **20** to iodine in a THF/water mixture resulted in a rapid lactonization to give an inseparable 3.5:1 mixture of the desired *trans*-**21** and the undesired *cis*-**21** isomers (Scheme 4). This result was in good agreement with the selectivity previously observed by us for a structurally similar amide substrate.[5] During the iodolactonization step, the chiral amine was released and recovered in 68% yield. Pure trans isomer was isolated after the next step, removal of iodine, which completed the synthesis of the target γ-butyrolactone **22** in five steps and 32% overall yield. This result is an improvement over the route previously developed in our laboratory, which required six steps and gave 29% yield of **2**.[4] It should be noted that besides being shorter, easier to scale-up, and more efficient, the new route also provides enantiomerically pure lactones, whereas the previous synthesis yielded products with 92% ee only.

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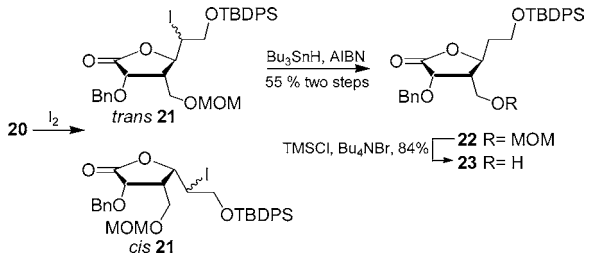
(22) The following Lewis acid/base combinations were tested: (a) $TiCl_4$ and $NEt(i\text{-}Pr)_2$, ref 19a; (b) $Yb(OSO_2CF_3)_3$ and $NEt(i\text{-}Pr)_2$, ref 19a; (c) $AlMe_3$ and K_2CO_3. Diederich, M.; Nubbermeyer, U. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1026−1028.

Scheme 4. Iodolactonization and Final Steps



To confirm the structure of **22**, the MOM group was selectively cleaved using TMSBr (prepared in situ). The ^{1}H and ^{13}C NMR spectra of the resulting alcohol **23** matched very well the spectra of racemic **23**, which was previously prepared by detritylation of **2**.[4] For the initial methodological studies reported herein, we chose (*S*)-**15b**, which was made from the relatively cheaper natural (*S*)-proline.[23] Our present choice would lead to modified nucleosides enantiomeric to natural RNA. This is by no means a problem because (*R*)-proline is also commercially available. In fact, modified nucleic acids enantiomeric to natural DNA and RNA may have unique applications in biotechnology and medicine.

In conclusion, we have developed a new and efficient asymmetric synthesis of chiral, enantiomerically pure *trans*-3,4-dialkyl-γ-lactones. To our knowledge, this is the first application of the three-component coupling[21] and acyl-Claisen[19] sequence in a total synthesis context. Because both (*S*)- and (*R*)-**15b** are readily available, our synthesis has the advantage over routes that start from carbohydrates that both enantiomers of **23**, and eventually **1**, can be prepared. Further optimization of the chiral auxiliary is expected to increase the efficiency of not only the three-component coupling but also the rearrangement and the iodolactonization steps, for both of which the use of similar amine auxiliaries has been reported.[24] Our synthesis may represent a general route to *trans*-3,4-dialkyl-γ-lactones because it is conceivable that other substituents at C-2, C-3, and C-4 can be introduced by the choice of appropriate small-molecule starting materials, e.g., acyl chloride **7**, alkyne **16**, and aldehyde **8**, respectively. Stereoselective synthesis of highly substituted γ-butyrolactones will be useful for construction of many natural products and synthetic intermediates, including the highly modified C-branched nucleosides that are targets of our laboratory.[1−5]

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Supporting Information Available: Experimental procedures, spectral data, and copies of ^{1}H and ^{13}C NMR data. This material is available free of charge via the Internet at http://pubs.acs.org.

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