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A General Synthetic Route Towards γ- and δ-Lactones. Total Asymmetric Synthesis of (–)-Muricatacin and the Mosquito Oviposition Pheromone *(5R,6S)*-6-Acetoxy-hexadecanolide.

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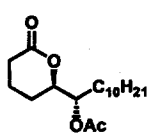
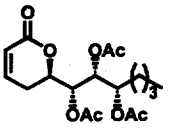
Abstract: Five (or six) membered asymmetric lactones are synthesized from γ-butyrolactone (or δ-valerolactone) in a straightforward way using the following reaction sequence: reduction, Wittig-Schlosser coupling, Sharpless asymmetric dihydroxylation, oxidation and lactonization. Thus, (–)-muricatacin is synthesized in six steps (43 % overall yield). Furthermore, (5*R*,6*S*)-6-acetoxy-hexadecanolide is prepared in eight steps (38 % overall yield) via a carbonate ester, utilizing a novel lactonization with inversion of stereochemistry.

A large number of biologically important natural products are derivatives of asymmetric γ- or δ-lactones.[1] In addition, these ubiquitous compounds are valuable synthetic key intermediates.[2]

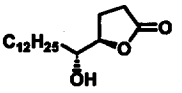
We would like to report a simple, general and efficient approach for the synthesis of optically pure hydroxylactones of the general formulae **1** or **2**, which are the common intermediates found in almost every synthetic route pertaining to lactones.



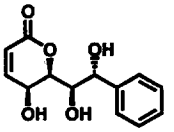
(5R,6S)-6-Acetoxy-hexadecanolide (mosquito pheromone)



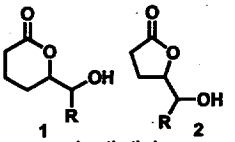
(+)-Boronolide (antimalarial)



(–)-Muricatacin (antitumor)



(+)-Goniotriol (antitumor)



(synthetic key intermediates)

In order to demonstrate the applicability of our methodology for the construction of δ-lactones, the total synthesis of the mosquito oviposition pheromone (5*R*,6*S*)-6-acetoxy-hexadecanolide, a popular synthetic target[3] and its epimeric analogue (5*S*,6*S*), has been performed as described on Scheme 1.[4] The key operations are a Wittig-Schlosser type chain extension for the formation of the *E*-alkene **4** which proceeds with very good selectivity (9:1) and a novel lactonization of carbonate **5** with inversion of stereochemistry. This transformation is achieved regio- and stereospecifically and in high yield upon heating substrate **5** in DMF for several hours.

The same strategy may be applied for the preparation of γ-lactones, an example of which is the syntheses of the anticancer natural products (–)-muricatacin and (+)-*epi*-muricatacin,[5] as depicted in Scheme 2. It is worth noting, that the small amount of *cis* isomer formed during Schlosser reaction is removed, either by kinetic control of the dihydroxylation, or by a recrystalization of the final lactone.

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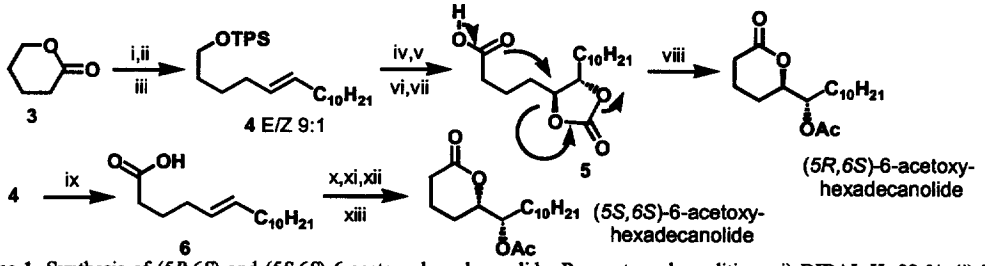
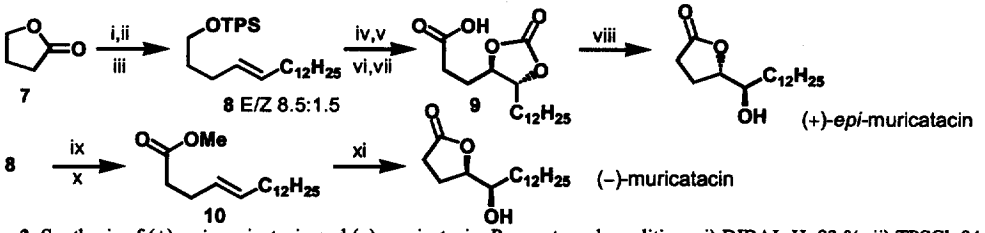


Scheme 1. Synthesis of (5*R*,6*S*) and (5*S*,6*S*)-6-acetoxy-hexadecanolide. Reagents and conditions: i) DIBAL-H, 88 %; ii) TPSCl, 82 %; iii) $Ph_3P^+(Br^-)C_{11}H_{23}$, *sec*-BuLi, 25°C, 1 h, then – 78°C, aldehyde, 10 min, then – 40°C, *sec*-BuLi, 15 min, then excess MeOH, 25°C, 2 h, 88 %; iv) AD-mix-α, 91 % (based on 60 % conversion); v) CDI, 96 %; vi) TBAF, 95 %; vii) $NaIO_4$, $RuCl_3$, 87 %; viii) DMF, 153°C, 18 h, then Ac_2O, Et_3N, cat. DMAP, 25°C, 82 %. $[\alpha]_D = -38.5$ ($c = 2.2$ in $CHCl_3$) [Lit.[3c,g] – 37.4, $c = 2.2$ in $CHCl_3$, – 36.7, $c = 1.8$ in $CHCl_3$]; overall yield 38 %; ix) Jones, 25°C, 12 h, 87 % (based on 15 % recovered material); x) MeOH, CSA, 95 %; xi) AD-mix-α, 91 % (based on 60 % conversion); xii) LiOH 3N/THF/MeOH (1/1/1), 100 %; xiii) Ac_2O, pyr, 80 %. $[\alpha]_D = -14.7$, ($c = 1.3$ in $CHCl_3$) [Lit.[3c] – 14.1 in $CHCl_3$]; overall yield 32 %. DIBAL-H = Diisobutylaluminum hydride, TPS = *t*Butyldiphenylsilyl, CDI = *N,N'*-carbonyldiimidazole.



Scheme 2. Synthesis of (+)-*epi*-muricatacin and (–)-muricatacin. Reagents and conditions: i) DIBAL-H, 93 %; ii) TPSCl, 84 %; iii) $Ph_3P^+(Br^-)C_{13}H_{27}$, *sec*-BuLi, 25°C, 1 h, then – 78°C, aldehyde, 10 min, then – 40°C, *sec*-BuLi, 15 min, then excess MeOH, 25°C, 2 h, 84 %; iv) AD-mix-β, 92 %; v) CDI, 97 %; vi) TBAF, 91 %; vii) $NaIO_4$, $RuCl_3$, 87 %; viii) DMF, 153°C, 3 h, 91 %. $[\alpha]_D = +27$ ($c = 1.9$ in $CHCl_3$) [Lit.[5b] +32, $c = 2$ in $CHCl_3$]; overall yield 42%; ix) Jones, 25°C, 12 h, 89 % (based on 18 % recovered material); x) MeOH, CSA, 97 %; xi) AD-mix-β, 92 %. $[\alpha]_D = -23.3$ ($c = 1.54$ in $CHCl_3$) [Lit.[5d] – 23.3, $c = 1.8$ in $CHCl_3$]; overall yield 43 %.

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[4] Spectral data (^1H, ^{13}C NMR, mass spectroscopy) and specific rotation of all compounds are in agreement with reported values.

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