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A General Approach To γ-Lactones via Osmium-Catalyzed Asymmetric Dihydroxylation. Synthesis of (-)- and (+)-Muricatacin.

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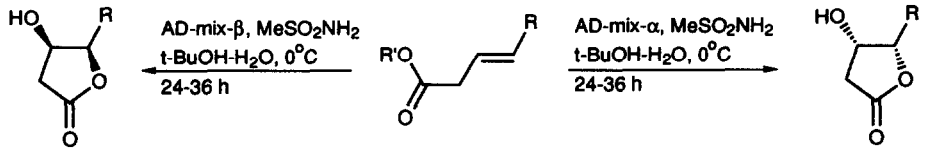
Abstract: Both enantiomers of hydroxy γ-lactones have been prepared highly enantioselectively (92-99% ee) using either AD-mix-β or AD-mix-α with both β,γ- and γ,δ-unsaturated esters. The method is exemplified by the three-step synthesis of (-) and (+)-muricatacin in 74% yield and >99% ee.

In this communication, we report that asymmetric dihydroxylation (AD) of β,γ- and γ,δ-unsaturated esters, using the recently introduced AD-mixes,[1] provides a very efficient and convenient method for direct preparation of optically active hydroxy γ-lactones.

Functionalized γ-lactones have attracted substantial attention in recent years due to their synthetic importance as building blocks in natural product synthesis,[2] as precursors to HIV-1 protease inhibitors,[3] and the fact that many of them are bioactive natural products.[4,5] We have found that both β,γ- and γ,δ-unsaturated esters, when subjected to the AD reaction, readily afford hydroxy γ-lactones. As shown in the Schemes, enantiomeric purities of both classes of lactones are excellent (92-99% ee) and all the γ-lactones are produced in good yield.

In the catalytic AD reaction of β,γ-unsaturated esters,[6] the resulting diols lactonize spontaneously to give 3-hydroxy γ-lactones (**2** and **3**,[7] Scheme 1). All the substrates (**1a-1c**) are commercially available, and the β,γ-unsaturated acids can also be easily prepared by modified Knoevenagel condensation of an aldehyde with malonic acid.[8]

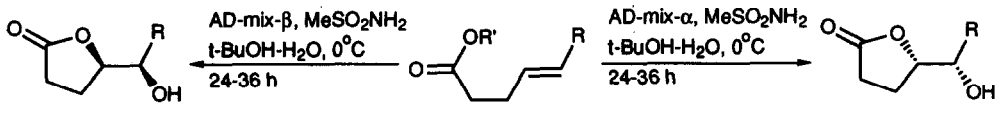
With γ,δ-unsaturated esters **4**,[9] the spontaneous cyclization of the diols under the AD reaction conditions is completely regioselective in the cases examined, since only γ-lactones **5** or **6**,[10] (no δ-lactones) were detected (Scheme 2).



2 (R,R) — **1** — **3** (S,S)

a) 60 % (96 % ee) — a) R = C_2H_5 R' = C_2H_5 — a) 65 % (92 % ee)
b) 80 % (97 % ee) — b) R = C_6H_{13} R' = CH_3 — b) 85 % (95 % ee)
c) 84 % (99 % ee) — c) R = C_6H_5 R' = CH_3 — c) 85 % (>99 % ee)

Scheme 1: AD of β,γ-unsaturated esters

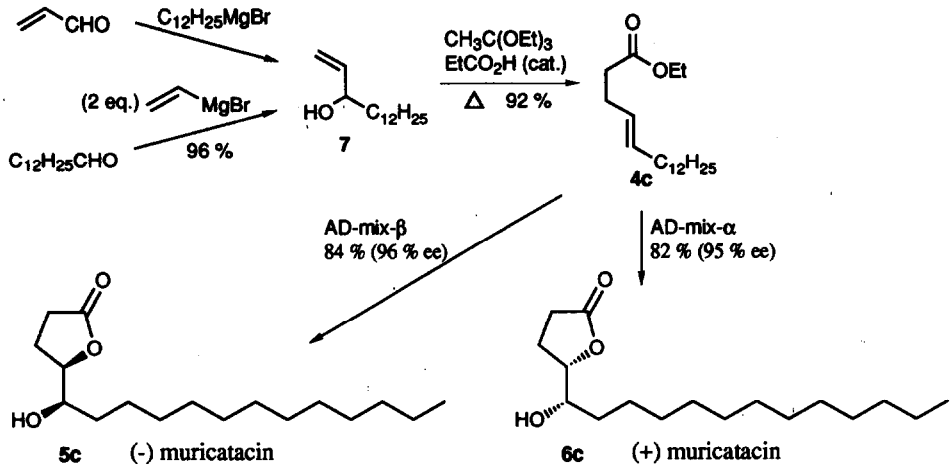


5 (R,R) — **4** — **6** (S,S)

a) 80 % (98 % ee) — a) R = C_3H_7 R' = C_2H_5 — a) 78 % (96 % ee)
b) 91 % (98 % ee) — b) R = C_5H_{11} R' = C_2H_5 — b) 91 % (96 % ee)
c) 84 % (96 % ee) — c) R = $C_{12}H_{25}$ R' = C_2H_5 — c) 82 % (95 % ee)
d) 92 % (97 % ee) — d) R = $PhCH_2$ R' = C_2H_5 — d) 90 % (96 % ee)

Scheme 2: AD of γ,δ-unsaturated esters

Many hydroxy-lactones, including those described above can serve as chiral building blocks in the synthesis of optically active natural products. Some of these lactones are themselves biologically active. For example, muricatacin, an acetogenin derivative that shows some cytotoxicity on human tumor cell lines, has been recently isolated from the seeds of *Annona muricata*.[5] The natural product is comprised of unequal proportions of (-)-(R,R)-5-hydroxyheptadeca-4-olide (**5c**) and its enantiomer, (+)-(S,S) (**6c**), with the former predominating. (-)-Muricatacin was synthesized in seventeen steps, starting with cyclooctyne and furane, including optical resolution of a racemic intermediate using a camphanoic ester.[11] (+)-Muricatacin was synthesized in four steps from L-glutamic acid.[12] An eight-step synthesis of both enantiomers has been recently reported.[13] Our approach produces either **5c** or **6c** in a three-step synthesis (Scheme 3). Addition of dodecylmagnesium bromide to acrolein afforded the allylic alcohol **7**.[14] Alternatively, **7** was obtained from the reaction of tridecanal with vinyl magnesium bromide. This alcohol was converted to the pure (E)-γ,δ-unsaturated ester **4c**[9] via the Johnson-Claisen rearrangement.[15] Finally, the two enantiomers, (-)- and (+)-muricatacin (**5c** and **6c**) were directly obtained upon dihydroxylation of **4** with either AD-mix-β or AD-mix-α. The enantiomeric purity of these two products (96% and 95% ee, respectively) was easily increased to essentially 100% ee by a single recrystallization from pentane-ether, as was determined by HPLC (using Pirkle 1-A chiral column with hexane:isopropanol, 95:5) and by ^{1}H NMR of their Mosher's esters.[16] Compounds **5c** (m.p. 73-74 °C, lit.[5] 50 °C, lit.[11] 72 °C, $[\alpha]_D$ = -23.14° (c = 2.36, $CHCl_3$), lit.[5] -16.1°, lit.[11] -22.9° (c = 1.1, $CHCl_3$)) and **6c** (m.p. 73-74 °C, lit.[12] 65 °C, $[\alpha]_D$ = +23.02° (c = 1.26, $CHCl_3$), lit.[12] +25° (c = 1.7, MeOH)) were found to be identical by ^{1}H NMR, ^{13}C NMR, IR, and MS, to an authentic sample of (-)-muricatacin.[17]



Scheme 3

Other bioactive compounds are found among the γ-lactones listed in Scheme 2. For example, compound **6b** which was found in strains of *Streptomyces griseus*[4d] has been previously synthesized in eight steps from D-ribose.[4e] Here it is prepared in a single step from the commercially available **4b**. Both **5d** and **6d** were isolated from the bacterium *Erwinia quercina* and found to be active lateral root-inducers[4c]. They were previously synthesized in rather long sequences from either glutamic acid[4c] or tartaric acid.[18] Here, both compounds are prepared with high enantiomeric purity in three steps from phenylacetaldehyde. In our accompanying paper[19] we describe the synthesis of all four isomers of disparlure, the sex attractant emitted by the female gypsy moth, *Porthetria dispar* (L.), with lactones **5** and **6** (R = $C_{10}H_{21}$, R' = Et) being key intermediates.

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References and notes

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6. In a typical AD reaction[1b] either AD-mix α or AD-mix β (1.4 g) is dissolved in *t*-butanol and water (5 ml of each) together with methanesulfonamide (95 mg, 1 mmol). The appropriate unsaturated ester (1 mmol) is added, the mixture is stirred at 0 °C for 24-36 h, sodium sulfite (1.5 g) is added, the mixture is stirred for 1 h at room temperature, and then extracted with ethyl acetate. Removal of solvent under reduced pressure followed by column chromatography affords the hydroxylactone product in the form of a white, crystalline solid.
7. **2a** and **3a**: **^{1}H NMR**: 4.49 (m, 1H), 4.31 (m, 1H), 2.97 (br s, 1H), 2.80 (dd, J = 17.6, 5.4, 1H), 2.55 (dd, J = 17.6, 4.0, 1H), 1.91 (m, 1H), 1.79 (m, 1H), 1.06 (t, J = 7.6, 3H). IR (neat): 3440, 1760, 1175 cm^{-1}. **MS** (FIB/CsI): 263 (M+Cs$^+$). **2a**: $[\alpha]_D$ +72.3° (c = 1.04, MeOH). **3a**: $[\alpha]_D$ -70.8° (c = 1.00, MeOH). **2b** and **3b**: **^{1}H NMR**: 4.48 (m, 1H), 4.37 (m, 1H), 2.80 (dd, J = 18.0, 5.4, 1H), 2.56 (dd, J = 18.0, 1.2, 1H), 2.05 (br s, 1H), 1.86 (m, 1H), 1.73 (m, 1H), 1.31 (m, 8H), 0.88 (t, J = 7.2, 3H). **IR** (neat): 3420, 1753, 1167 cm^{-1}. **MS** (FIB/NaI): 209 (M+Na+), 187 (M+H+). **2b**: $[\alpha]_D$ +54.3° (c = 1.08, MeOH). **3b**: $[\alpha]_D$ -53.4° (c = 1.12, MeOH). **2c** and **3c**: **^{1}H NMR**: 7.42 (m, 5H), 5.53 (d, J = 3.6, 1H), 4.64 (m, 1H), 2.92 (dd, J = 17.6, 5.2, 1H), 2.76 (dd, J = 17.6, 3.6, 1H), 1.39 (br s, 1H). **IR** (KBr): 3390, 1750, 1155 cm^{-1}. **MS** (FIB/NaI): 201 (M+Na+) **2c**: $[\alpha]_D$ -35.7° (c = 0.92, MeOH). **3c**: $[\alpha]_D$ +35.6° (c = 0.98, MeOH). All optical rotation values correspond to non-recrystallized products.
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9. **4c**: **^{1}H NMR**: 5.40 (m, 2H), 4.11 (q, J = 7.2, 2H), 2.31 (m, 4H), 1.95 (q, J = 6.7, 2H), 1.25 (m, 23H), 0.86 (t, J = 7.2, 3H). **^{13}C NMR**: 173.25, 131.82, 127.85, 60.18, 34.41, 32.48, 31.89, 29.75, 29.52, 29.40, 29.08, 27.96, 22.66, 14.22. **4d**: **^{1}H NMR**: 7.28 (m, 2H), 7.18 (m, 3H), 5.61 (m, 1H), 5.53 (m, 1H), 4.11 (q, J = 7.2, 2H), 3.32 (d, J = 6.4, 2H), 2.36 (m, 4H), 1.24 (t, J = 7.2, 3H).
10. **5a** and **6a**: **^{1}H NMR**: 4.42 (m, 1H), 3.60 (m, 1H), 2.58 (m, 2H), 2.25 (m, 1H), 2.13 (m, 1H), 1.95 (br s, 1H), 1.54 (m, 4H), 0.95 (t, J = 7.2, 3H). **IR** (neat): 3400, 1764, 1194 cm^{-1}. **5a**: $[\alpha]_D$ -38.4° (c = 1.21, $CHCl_3$). **6a**: $[\alpha]_D$ +37.9° (c = 1.12, $CHCl_3$). **5b** and **6b**: **^{1}H NMR**: 4.40 (m, 1H), 3.56 (m, 1H), 2.67-2.54 (m, 2H), 2.25 (m, 1H), 2.14 (m, 1H), 1.97 (br s, 1H), 1.30-1.54 (m, 8H), 0.88 (t, J = 6.8, 3H). IR (neat): 3432, 1771, 1192 cm^{-1}. **5b**: $[\alpha]_D$ -31.6° (c = 1.43, $CHCl_3$). **6b**: $[\alpha]_D$ +30.8° (c = 1.41, $CHCl_3$). **5d** and **6d**: **^{1}H NMR**: 7.29 (m, 5H), 4.46 (dt, J = 7.2, 3.2, 1H), 3.84 (dt, J = 6.8, 3.2, 1H), 2.92 (d, J = 6.8, 2H), 2.64 (dt, J = 8.8, 2.4, 1H), 2.51 (dt, J = 8.8, 18.0, 1H), 2.22 (m, 2H), 1.95 (br s, 1H). **IR** (neat): 3430, 1771, 1192 cm^{-1}. **5d**: $[\alpha]_D$ -57.6° (c = 1.14, $CHCl_3$). **6d**: $[\alpha]_D$ +56.7° (c = 0.97, $CHCl_3$). All optical rotation values correspond to non-recrystallized products.
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14. **7**: **^{1}H NMR**: 5.84 (ddd, J=16.7, 10.5, 5.7, 1H), 5.19 (d, J=17.2, 1H), 5.08 (d, J=10.5, 1H), 4.07 (q, J=6.5, 1H), 1.67 (br s, 1H), 1.49 (m, 1H), 1.24 (m, 21H), 0.89 (t, J=6.5, 3H). **^{13}C NMR**: 141.33, 114.44, 73.23, 37.02, 31.89, 29.71, 29.26, 25.35, 22.66, 14.08.
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