Keywords: anthraquinones · carbohydrates · DNA hybrids · DNA recognition · intercalations

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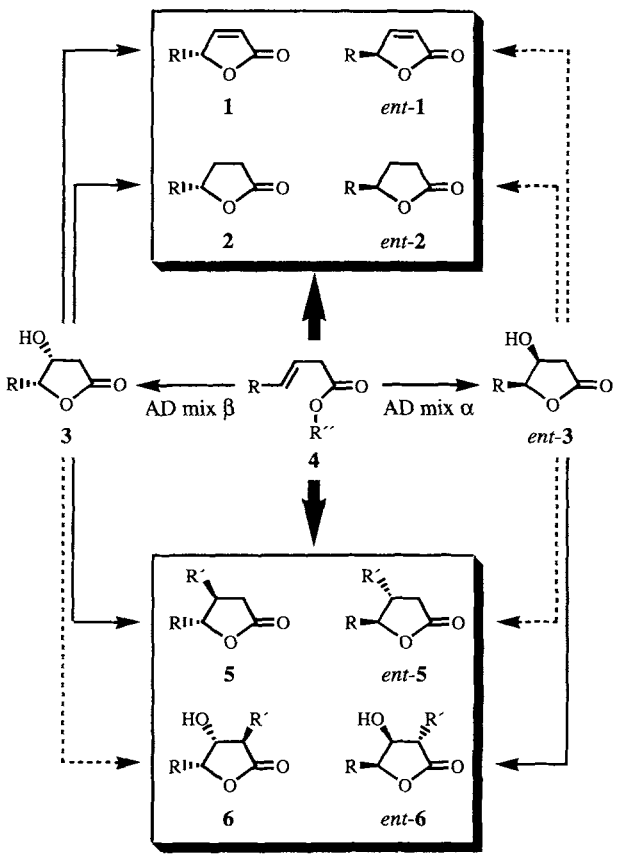
Synthesis of Optically Active Butenolides and γ-Lactones by the Sharpless Asymmetric Dihydroxylation of β,γ-Unsaturated Carboxylic Esters**

Christian Harcken and Reinhard Brückner*

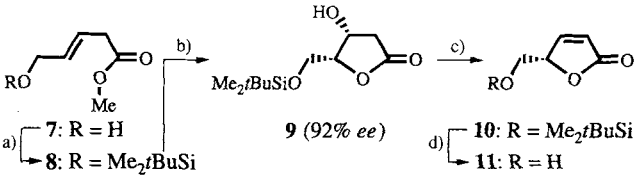
The Sharpless asymmetric dihydroxylation ("AD") of olefins is an indispensable tool for contemporary organic synthesis.[1] Frequently, the obtained 1,2-diols are not yet the desired target molecules. Rather, they are so profoundly modified by follow-up reactions that it may no longer be clear from the structures of the final products how well an AD served in their construction. The present study reveals that enantiomerically pure or enantiomerically enriched γ-chiral butenolides and γ-chiral γ-lactones—for which many syntheses are known, but more efficient ones are continuously being sought[2,3]—must be considered interesting products of the AD, too (Scheme 1). Specifically, ADs of β,γ-unsaturated esters **4** provided (in accordance with the scarce literature precedence[4,5]) lactonized dihydroxylation products, that is,



Scheme 1. Furanone derivatives accessible in two or three steps from **4**. Concrete examples for the reactions marked with solid arrows are given in Schemes 2–5. The dashed arrows refer to analogous transformations in the respective enantiomeric series that, however, have not yet been performed.

the compounds **3** or their enantiomers *ent*-**3** (78% ≤ *ee* ≤ 97%). From these, we have prepared to date chiral butenolides **1**/*ent*-**1**, monosubstituted γ-lactones **2**/*ent*-**2**, disubstituted γ-lactones **5**/*ent*-**5**, and trisubstituted γ-lactones **6**/*ent*-**6**. The transformations used are exemplified by enantioselective syntheses of the ranunculin aglycon (**11**; 92% *ee*; Scheme 2), the pheromone dodecanolide (**16**; 95% *ee*; Scheme 3), *trans* quercus lactone (**21**; 97% *ee*; Scheme 4), and one of the *epi*-blastmycinones (**25**; 78% *ee*; Scheme 5).

Our novel approach to γ-chiral butenolides **1** on the basis of the transformation type-**4**-ester →type-**3**-lactone is shown in Scheme 2. First, the known hydroxyester **7**[6] was O-silylated



Scheme 2. a) *t*BuMe$_2$SiCl (1.5 equiv), imidazole (3.0 equiv), CH_2Cl_2, 0°C, 30 min; 84%. b) AD mix-β (1.40 g per mmol of **8**), methanesulfonyl amide (1.0 equiv), *t*BuOH/H_2O (1/1), addition of **8**, 0°C, 36 h; 88%. c) NEt_3 (2.1 equiv), methanesulfonyl chloride (1.1 equiv), CH_2Cl_2, 0°C, 1 h; 72%. d) HF/pyridine complex (70%, 0.50 mL per mmol of **10**), THF, 0°C, 16 h; silica gel, 15 min; 85%.

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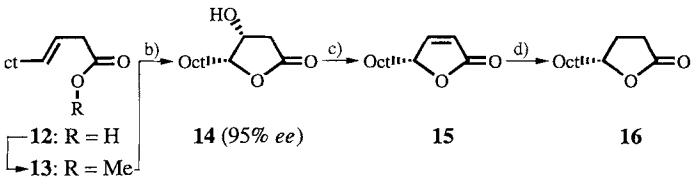
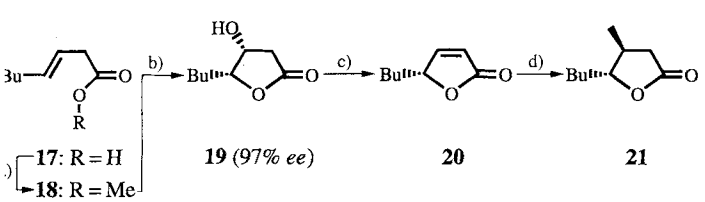
to form the β,γ-unsaturated ester **8**.[7] Then the compound was asymmetrically dihydroxylated by treatment with AD mix β to provide after purification by flash chromatography on silica gel[8] the *tert*-butyldimethylsilylated γ-lactone **9**[9] with 92% *ee*.[10] Mesylation with mesyl chloride/triethylamine followed by the spontaneous β-elimination of methanesulfonic acid introduced the C=C bond of the silylated butenolide **10**. Deprotection with HF/pyridine gave the ranunculin aglycon **11**.[11,12]

Our type-**4**-ester →type-**3**-lactone approach to chiral monosubstituted γ-lactones **2** is illustrated in Scheme 3 by an enantioselective synthesis of the rove beetle pheromone (+)-dodecanolide (**16**).[13] We started with a decarboxylative deconjugating Knoevenagel condensation between decanal and malonic acid; this provided the β,γ-unsaturated acid **12** predominantly as the desired *trans* isomer.[14] Four more steps (62% yield) led to the target structure **16**. They were: 1) esterification (→methyl ester **13**), 2) AD with AD mix β (→lactone **14**; 95% *ee*[10]), 3) mesylation/β-elimination (→butenolide **15**), and 4) Pd-catalyzed hydrogenation.[15]



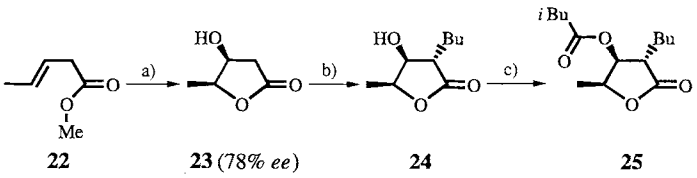
Scheme 3. a) MeOH (3.0 equiv), camphorsulfonic acid (1.0 mol%), $CHCl_3$, removal of water by azeotropic distillation, 12 h; 90%. b) AD mix β (1.40 g per mmol of **13**), methanesulfonyl amide (1.0 equiv), *t*BuOH/H_2O (1/1), addition of **13**, 0°C, 48 h; 81%. c) NEt_3 (2.1 equiv), methanesulfonyl chloride (1.1 equiv), CH_2Cl_2, 0°C, 15 min; 91%. d) Pd (10% on charcoal, 5 mol%), H_2 (3 bar), EtOAc, room temperature, 12 h; 94%.

Scheme 4 illustrates the AD-mediated type-**4**-ester →type-**3**-lactone approach to chiral disubstituted γ-lactones **5** by the hitherto shortest enantioselective synthesis[16] of *trans* quercus lactone (**21**).[17] This compound is formed in whisky barrels manufactured from oak-wood and contributes to the taste of the liquors stored therein. Acid **17**[14] was condensed with methanol and the resulting methyl ester **18** treated with AD mix β. Lactone **19** was obtained in 92% yield and with 97% *ee*.[18] Dehydration with the mesyl chloride/triethylamine mixture, which was also used in the **9**→**10** and **14**→**15** conversions, yielded butenolide **20**. Me_2CuLi added to this compound exclusively from the less hindered face, and we isolated the desired *trans*-configured 1,4-addition product **21** (the *trans* quercus lactone, also termed *trans* oak lactone or *trans* whisky lactone) and none of its *cis* isomer. The overall yield of this sequence was 47%.



Scheme 4. a) MeOH (3.0 equiv), camphorsulfonic acid (1.0 mol%), $CHCl_3$, removal of water by azeotropic distillation, 6 h; 76%. b) AD mix β (1.40 g per mmol of **18**), methanesulfonyl amide (1.0 equiv), *t*BuOH/H_2O (1/1), addition of **18**, 0°C, 36 h; 92%. c) NEt_3 (2.1 equiv), methanesulfonyl chloride (1.1 equiv), CH_2Cl_2, 0°C, 15 min; 87%. d) CuI (1.5 equiv), Et_2O, 0°C; addition of MeLi (3.0 equiv); cooling to −78°C; addition of **20** in Et_2O, 1.5 h; 77% of **21**.

Scheme 5 shows how treatment of the commercially available methyl pentenoate **22** with AD mix α makes the type-**4**-ester →type-**3**-lactone conversion a remarkably efficient synthesis of chiral trisubstituted γ-lactones **6**. Not



Scheme 5. a) AD mix α (1.40 g per mmol of **22**), *t*BuOH/H_2O (1/1), addition of **22**, 0°C, 5 d; 40%. b) LDA (3.0 equiv), THF, −78°C, 2 h; BuI (1.5 equiv) in THF/DMPU 1/1 (3 mL per mmol of BuI), −35°C, 20 h; 53% of **24**. c) 3-Methylbutanoyl chloride (1.5 equiv), CH_2Cl_2/pyridine 5/1, room temperature, 6 h; 83%.

unexpectedly,[19] the dihydroxylation product **23** exhibited only 78% *ee*.[10] With reference to the next step, it is known that in HMPA-containing THF (HMPA = hexamethyl phosphoric triamide) the α-alkylation of dilithiated β-hydroxy-γ-lactones akin to compound **23** occurs such that the α-substituent is oriented almost exclusively *trans* with respect to the β-OH group.[20] We were pleased to find that in 4:1 THF/DMPU[21] (DMPU = dimethylpropyleneurea) the butylation of the dilithiated β-hydroxylactone **23** itself also delivered only the *trans*-alkylated lactone **24** (53% yield) and no *cis* isomer at all. Acylation with isovaleroyl chloride led to the isovalerate **25**. As an epimer of blastmycinone, the antimycin A_3 degradation product, compound **25** had previously been synthesized several times, but with less rigorous stereocontrol.[22]

Several other AD-mediated butenolide and butyrolactone syntheses that exploit the ready availability of type-**4** esters[14] and employ type-**4**-ester →type-**3**-lactone conversions are under investigation in our laboratory.

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[18] **19**: *trans*-octenoate **17** (2.66 mL, 2.34 g, 15.0 mmol) was added to a mixture of *t*BuOH (50 mL), H_2O (50 mL), AD-mix β (21.0 g), and methanesulfonyl amide (1.43 g, 15.0 mmol, 1.0 equiv). The solution was stirred for 36 h at 0°C. After the addition of saturated Na_2SO_3 solution (2 mL) the mixture was extracted with *t*BuOMe (3 × 100 mL). The extracts were dried over Na_2SO_4, and the solvent was removed. Flash-chromatography on silica gel (ref. [8]; 5 cm, petroleum ether/*t*BuOMe 1:1 → 1:3) yielded **19** (2.20 g, 92%) as a colorless liquid. $[\alpha]_D^{25} = 70.8°$ ($c = 1.36$ in MeOH). Chiral capillary gas chromatography (ref. [10]) at 130°C of **19** (R_T 75.6 min) vs. its enantiomer (R_T 77.3 min) revealed 97% *ee* in favor of **19**. IR (neat): $\tilde{\nu}$ = 3450, 2960, 2870, 1760, 1205, 1170, 1085, 1015, 975 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.94$ (t, $J_{4',3'} = 7.0$, 4'-H_3), 1.32–1.56 (m, 2'-H_2, 3'-H_2), 1.66–1.94 (m, 1'-H_2), AB signal ($\delta_A = 2.55$, $\delta_B = 2.79$, $J_{AB} = 17.9$, additionally split by $J_{B,4} = 5.5$, 3-H_2), partially overlapped by 2.61 (br. s, OH), 4.37 (ddd, $J_{5,1'\text{-}H(1)} = 8.9$, $J_{5,1'\text{-}H(2)} = 5.8$, $J_{5,4} = 3.8$, 5-H), 4.48 (dd, $J_{4,3\text{-}H(B)} \approx J_{4,5} \approx 4.4$, 4-H). C,H analysis calcd for $C_8H_{14}O_3$ (158.2): C 60.74, H 8.92; found: C 60.59, H 9.15.
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A Hexaimidazole Ligand Binding Six Octahedral Metal Ions To Give an Infinite 3D α-Po-Like Network Through Which Two Independent 2D Hydrogen-Bonded Networks Interweave**

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The current intense activity in the area of crystal engineering can be traced back to a number of pioneering studies, an important one of which concerns the hexa-host clathrates introduced and elaborated by MacNicol et al. about twenty years ago.[1] This approach, which offered a very appealing element of deliberate design, led to the isolation and structural characterization of a wide range of new crystalline inclusion compounds by the use of host molecules based on benzene rings hexasubstituted by flexible but bulky side arms such as arylthio-, aryloxy-, and arylmethyl- groups. Weak van der Waals interactions were responsible in these cases for binding the hexa-host molecules together into a crystal lattice that left large cavities for guest molecules. Herein we make use of the hexa-host approach, but the six benzene substituents are terminated by outwardly directed imidazole donor ligands which can then, in principle, be bound together into a crystalline lattice by coordinate bonds to metal ions. Metal–ligand bonding in these systems may provide much better control and strength in assembling the hexa-hosts into lattices with larger cavities than could possibly be achieved by using the weaker and less predictable van der Waals interactions.

The ligand used here is hexakis(imidazol-1-ylmethyl)benzene (hkimb; **1**). Imidazole termini were deliberately chosen because they provide strong coordinate bonds and are small enough to allow six to assemble around an octahedrally coordinated metal ion (in contrast, for example, to pyridine donors).

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