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Stereopure 1,3-butadiene-2-carboxylates and their conversion into non-racemic α-alkylidenebutyrolactone natural products by asymmetric dihydroxylation

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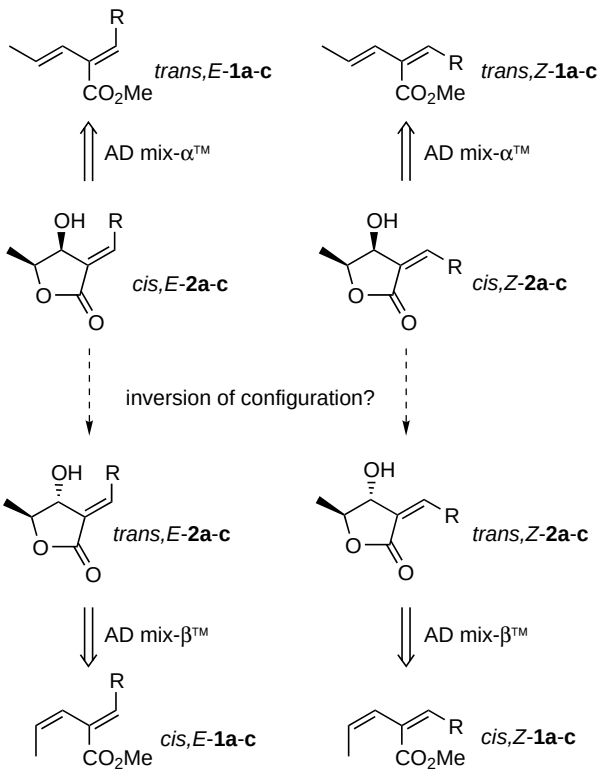
Abstract—Dienoic esters **1** with the four possible permutations of the C=C configurations were prepared in two steps via non-stereoselective aldol additions followed by stereospecific β-eliminations. Sharpless dihydroxylations of these esters yielded natural and unnatural α-alkylidene-β-hydroxybutyrolactones **2**. Among these were synthetic dihydromahubanolide B (*cis*,*Z*-**2a**), isodihydromahubanolide B (*cis*,*E*-**2a**) and, for the first time, litsenolide D_1 (*ent*-*trans*,*Z*-**2b**) and the enantiomer *trans*,*E*-**2b** of litsenolide D_2. Competitively, dihydroxyesters **10** were formed.

Naturally occurring α-alkylidene-β-hydroxylactones **2** occur with all conceivable substitution patterns *cis*,*E*-**2**, *cis*,*Z*-**2**, *trans*,*E*-**2** and *trans*,*Z*-**2** (Scheme 1). They comprise (−)-isodihydromahubanolide B (*cis*,*E*-**2a**), (−)-dihydromahubanolide B (*cis*,*Z*-**2a**), (+)-isodihydromahubanolide A (*trans*,*E*-**2a**), (−)-litsenolide D_2 (*ent*-*trans*,*E*-**2b**), (−)-litsenolide C_2 (*ent*-*trans*,*E*-**2c**), (+)-dihydromahubanolide A (*trans*,*Z*-**2a**), (−)-litsenolide D_1 (*ent*-*trans*,*Z*-**2b**), (−)-litsenolide C_1 (*ent*-*trans*,*Z*-**2c**), and analogous compounds containing C=C or C≡C bonds in the side-chain R. The (iso)dihydromahubanolides stem from the wood of *Clinostemon mahuba* in Brazil[1] and the litsenolides from the leaves of *Litsea japonica* in Japan.[2]

We have shown that the asymmetric dihydroxylation ('AD')[3] of *trans*-configurated β,γ-unsaturated esters leads, via *cis*-configurated β-hydroxy-γ-lactones,[4] to structurally diverse, optically active γ-lactones.[5] We now studied whether the α,β′,β,γ-unsaturated esters **1** are dihydroxylated at the $C^{\beta}=C^{\gamma}$ bond in a similar fashion (Scheme 1). This could furnish the four diastereomers of type-**2** lactones in optically active form directly or after Mitsunobu inversion of the allylic OH group. Both in the *trans*- and the *cis*-configurated esters **1** the intended site of attack of the AD reagent was a disubstituted C=C bond (which is—differently substi-



Scheme 1.

Keywords: asymmetric synthesis; elimination reactions; esters; hydroxylation; lactones.

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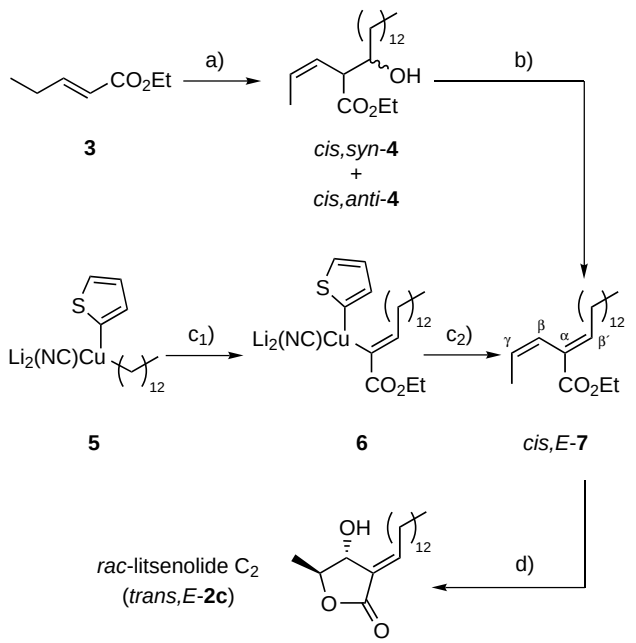
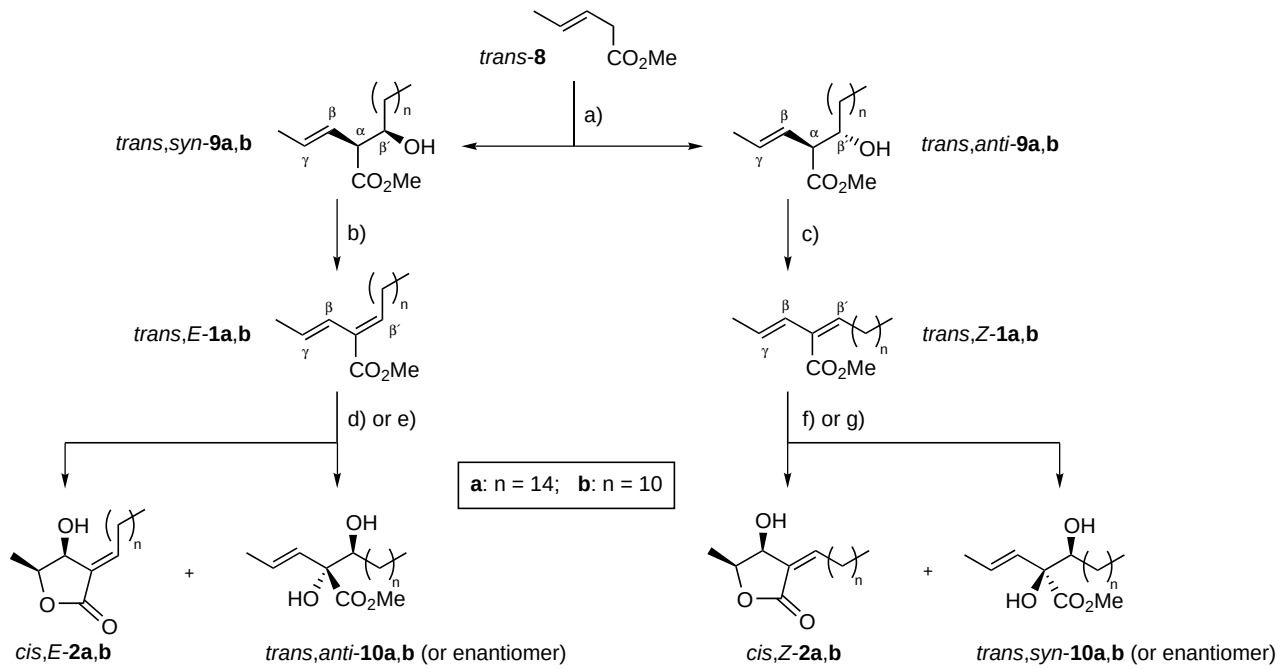


Scheme 2. (a) LDA, HMPA/THF, −78°C; RCHO.[7b] (b) MsCl, NEt_3, CH_2Cl_2; KH, THF, 0→20°C; 92%.[7b] (c_1) HC≡CCO$_2$Et; (c_2) *cis*-BrHC=CHMe, $Pd(PPh_3)_4$ (cat.).[7a] (d) OsO_4 (20 mol%), NMO, *t*-BuOH/acetone/H_2O, 20°C, 1 day; HCl, 4 h; 66%.[7b]

tuted—usually dihydroxylated with 90–99% *ee* in the *trans*-series and with 20–80% *ee* in the *cis*-series[3]). However, AD reactions of esters akin to **1** *may* occur at the acceptor-substituted, i.e. C^{α}=$C^{\beta'}$, bond rather than at the acceptor-free, i.e. C^{β}=C^{γ}, bond.[6] Fortunately, this is not forcedly so: Two syntheses of racemic litsenolide C_2 (*trans*,*E*-**2c**) via the OsO_4/NMO-mediated dihydroxylation of the dienoic ester *cis*,*E*-**7** (Scheme 2) relied upon the same C^{β}=C^{γ} selectivity which we required.[7]

The first objective of this study[8] was to obtain the isomerically pure α,β′,β,γ-unsaturated esters *trans*,*E*-**1** and *trans*,*Z*-**1** (Scheme 3).[9] As the first step, the lithium enolate of ester *trans*-**8** was hydroxyalkylated with hexadecanal. The 55:45 mixture of the *trans*,*syn*- and *trans*,*anti*-diastereomers of the resulting β-hydroxyester **9a** was separated by flash chromatography on silica gel,[10] the minor diastereomer preceding the major. Similarly, the aldol addition between lithiated ester *trans*-**8** and dodecanal furnished the β-hydroxyesters *trans*,*syn*-**9b** and *trans*,*anti*-**9b** as a readily separable 66:34 mixture. Being unaware of comprehensive ^{1}H NMR analyses of all diastereomers of an unsaturated hydroxyester like compound **9b**, pertinent $\delta_{1\text{-H}}$ and $^3J_{H,H}$ values are collected in Table 1.[11]

Dehydrations of β-hydroxyesters can be *syn*- or *anti*-selective but mixed mechanisms or subsequent isomerizations can interfere with obtaining good stereocontrol. This is a notorious problem when the *Z*-configurated, less stable α,β-unsaturated ester is to be formed—no matter whether by a *syn*-elimination from a *syn*-configurated β-hydroxyester[12] or by an *anti*-elimination from its *anti*-isomer.[13] We achieved *highly anti*-selective dehydrations of all hydroxyesters *trans*,*syn*-



Scheme 3. (a) LDA (1.1 equiv.), THF, −78°C, 30 min; RCHO (0.95 equiv.), →0°C, 30 min; 47% *trans*,*syn*-**9a**, 38% *trans*,*anti*-**9a**; 57% *trans*,*syn*-**9b**, 29% *trans*,*anti*-**9b**. (b) PPh_3 (2.0 equiv.), DEAD (2.0 equiv.), THF, −40→20°C, 5 h; **a**: 91% (*E*/*Z* 98:2); **b**: 86% (*E*/*Z* 98:2). (c) Same as (b); **a**: 92% (*Z*/*E*>98:2); **b**: 82% (*Z*/*E* 98:2). (d) AD-mix α™ (1.4 g/mmol), $MeSO_2NH_2$ (1.0 equiv.), *t*-BuOH/H_2O 1:1, 0°C, 6 days; 21% *cis*,*E*-**2a** (45% b.o.r.s.m.; 78% *ee*), 10% *trans*,*anti*-**10a** (21% b.o.r.s.m.), 53% *trans*,*E*-**1a**; 28% *cis*,*E*-**2b**, 7% *trans*,*anti*-**10b**. (e) $K_3Fe(CN)_6$ (3.0 equiv.), K_2CO_3 (3.0 equiv.), $(DHQ)_2PHAL$ (10 mol%), $K_2OsO_3(OH)_2$ (2.0 mol%), $MeSO_2NH_2$ (1.0 equiv.), *t*-BuOH/H_2O (1:1), 0°C, 24 h; 28% *cis*,*E*-**2a** (68% *ee*), 8% *trans*,*anti*-**10a**. (f) Same as (d); 4 days; 49% *cis*,*Z*-**2a**, 29% *trans*,*syn*-**10a**; 65% *cis*,*Z*-**2b**, 11% *trans*,*syn*-**10b**. (g) Same as (e); 24% *cis*,*Z*-**2a**, 18% *trans*,*syn*-**10a**.

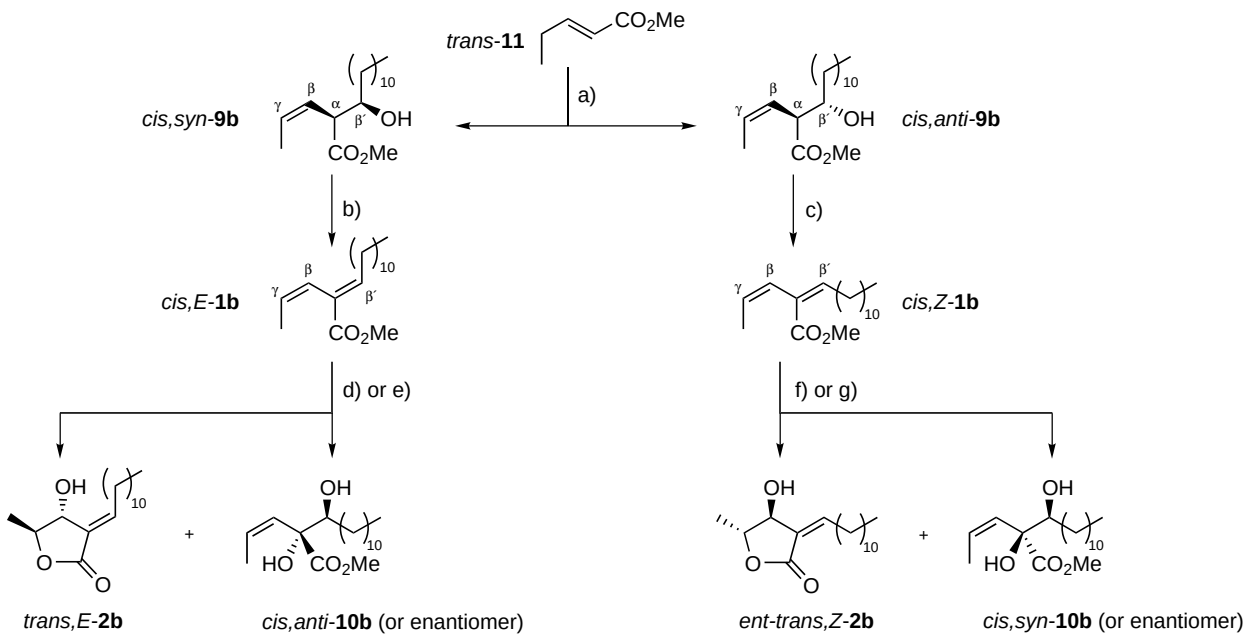
Table 1. Selected ^{1}H NMR data ($CDCl_3$, 300 MHz) of aldol adducts **9b**

Compound	$\delta_{\gamma\text{-H}}$	$\delta_{\beta\text{-H}}$	$\delta_{\alpha\text{-H}}$	$\delta_{\beta'\text{-H}}$	$J_{\gamma,\beta}$	$J_{\beta,\alpha}$	$J_{\alpha,\beta}$
trans,*syn*-**9b**	5.67	5.55	3.01	3.86	15.4	9.0	4.7
trans,*anti*-**9b**	5.65	5.41	3.05	3.78	15.5	9.0	8.3
cis,*syn*-**9b**	5.82	5.57	3.43	3.93	10.7	10.0	4.4
cis,*anti*-**9b**	5.71	5.38	3.43	3.83	10.8	9.1	9.1

and *trans*,*anti*-**9a**,**b** by treatment with excess PPh_3/diethyl azodicarboxylate (THF, −40°C→rt; Scheme 3):[14] β-hydroxyesters *trans*,*syn*-**9a**,**b** yielded dienoic esters *trans*,*E*-**1a**,**b** (86–91%, *E*/*Z* 98:2) while β-hydroxyesters *trans*,*anti*-**9a**,**b** provided esters *trans*,*Z*-**1a**,**b** (82–92%, *Z*/*E*≥98:2). The configuration of the newly formed C=C bond was deduced from $\delta_{3\text{-H}}=6.60$ (*Z*) or 5.78 (*E*).

Dienoic esters **1a**,**b** were dihydroxylated using AD-mix α™ and dienoic esters **1a** additionally by using 10 mol% $(DHQ)_2PHAL$ (instead of 1 mol% in AD-mix α™) and 2.0 mol% $K_2OsO_3(OH)_2$ (instead of 0.2 mol% in AD-mix α™) (Scheme 3). Such an 'improved procedure'[15] had increased the *ee* of the AD of another substrate containing a methyl-substituted C=C bond from 80 to 94%.[5e] The α-alkylidene-β-hydroxylactones **2a**,**b** resulted in 21–65% yields. Competing AD of the $C^{\alpha}=C^{\beta}$ bond furnished dihydroxyesters **10a**,**b** in 7–18% yield. Sparing solubility of the highly lipophilic substrates **1** in the polar reaction mixture contributed to the sub-optimal yields; for example, we re-isolated ester *trans*,*E*-**1a** in up to 53% yield. The *ee* of hydroxylactone *cis*,*E*-**2a** was 78%, according to chiral HPLC, when formed under standard AD conditions [21% yield; 45% based on recovered starting material ('b.o.r.s.m.')] or 68% using the modified AD procedure (28% yield). From the specific rotation $[\alpha]_D=-38.2$ for a 76% *ee* 90:10 mixture of hydroxylactones *cis*,*Z*-/*cis*,*E*-**2a**[16] and the specific rotation $[\alpha]_D=-93.3$ of natural *cis*,*E*-**2a**,[1b] one deduces $[\alpha]_D\approx(-38.2+0.1\times0.76\times93.3)/(0.9\times0.76)=-45.5$ for *cis*,*Z*-**2a**.[17] Our specimen of *cis*,*Z*-**2a** possessed $[\alpha]_D=-30$ so that one infers $ee\approx(-30)/(-45.5)=66\%$.

Overall, optically active isodihydromahubanolide B (*cis*,*E*-**2a**) and dihydromahubanolide B (*cis*,*Z*-**2a**) were obtained after only three synthetic steps. This compares well with previous syntheses which had led to a *cis*,*Z*-/*cis*,*E*-**2a** mixture (separable only by preparative TLC; 14 steps from dimethyl L-tartrate[18]), to both *cis*,*E*- and *cis*,*Z*-**2a** (13 steps from D-glucose bisacetonide[19]), to a 90:10 *cis*,*Z*-/*cis*,*E*-**2a** mixture (76% *ee*; seven steps from 1-octadecyne[16]) or to a 75:25 *cis*,*E*-/*cis*,*Z*-**2a** mixture (eight steps from ethyl *S*-lactate[20]).



Scheme 4. (a) LDA (1.23 equiv.), THF/DMPU 8:1, −78°C, 30 min; dodecanal (1.4 equiv.), →0°C, 1 h; 49% *cis*,*syn*-**9b**, 38% *cis*,*anti*-**9b**. (b) PPh_3 (2.0 equiv.), DEAD (2.0 equiv.), THF, −20→20°C, 4 h; 81% (*E*/*Z*>99:1, *cis*/*trans* 97:3). (c) Same as (b); 83% (*Z*/*E*>99:1, *cis*/*trans* 95:5). (d) AD-mix α™ (1.4 g/mmol), $MeSO_2NH_2$ (1.0 equiv.), *t*-BuOH/H_2O 1:1, 5°C, 7 days; 22% *trans*,*E*-**2b** (47% b.o.r.s.m.; 28% *ee*), 15% *cis*,*anti*-**10b** (32% b.o.r.s.m.), 53% *cis*,*E*-**1b**. (e) $K_3Fe(CN)_6$ (3.0 equiv.), K_2CO_3 (3.0 equiv.), $(DHQ)_2PHAL$ (10 mol%), $K_2OsO_3(OH)_2$ (2.0 mol%), $MeSO_2NH_2$ (1.0 equiv.), *t*-BuOH/H_2O (1:1), 0°C, 24 h; 15% *trans*,*E*-**2b** (36% *ee*), 14% *cis*,*anti*-**10b**. (f) Same as (d); 28% *trans*,*Z*-**2b** (43% b.o.r.s.m.; 16% *ee*), 15% *cis*,*syn*-**10b** (23% b.o.r.s.m.), 34% *cis*,*Z*-**1b**. (g) Same as (e); 30% *trans*,*Z*-**2b** (16% *ee*), 6% *cis*,*syn*-**10b**.

The OH group of lactone *cis*,*E*-**2b** stayed inert under Mitsunobu conditions[21] even after prolonged stirring (2 days) at elevated temperature (80°C). Treatment with PBu_3, tetramethyl azodicarboxamide and $PhCO_2H$[22] furnished 47% of a 87:13 *E*/*Z*-mixture of the 1,2-elimination product, i.e. α-dodecylidene-γ-methyl-Δ^4-butenolide. Attempted S_N reactions with the mesylate derived from *cis*,*E*-**2b** gave mixtures of the S'_N-product (KO_2, DMSO, rt, 12 h[23]) and the 1,4-elimination product (KOAc, 18-crown-6, DMF, 0°C, 8 h[24]). Lactone *cis*,*Z*-**2b** resisted attempts of configurational inversion, too.

Circumventing this inertia, α-alkylidene-β-hydroxylactones *trans*,*E*-**2b** and *trans*,*Z*-**2b** were synthesized from ester *trans*-**11** by the strategy of Scheme 3, i.e. by an aldol addition (^{1}H NMR data: Table 1) followed by stereospecific β-eliminations and standard or modified ADs (Scheme 4). Even the PPh_3/DEAD-mediated dehydration delivering the hindered dienoic ester *cis*,*Z*-**1b** was highly *anti*-selective (→>99:1 *Z*/*E*- and 95:5 *cis*/*trans*-ratios). The AD reactions of *cis*,*E*- and *cis*,*Z*-**1b** produced hydroxylactones *trans*,*E*- and *ent*-*trans*,*Z*-**2b** in only 15–22 and 28–30% yield, respectively. This seems to be caused by lacking solubility—53% dienoic ester *cis*,*E*-**1b** and 34% *cis*,*Z*-**1b** were re-isolated—and by competing ADs of the C^{α}=C^{β} bond—6–15% dihydroxyesters **10a**,**b** were found. According to chiral HPLC, the *ee* of lactone *trans*,*E*-**2b** was 28–36% and the *ee* of *ent*-*trans*,*Z*-**2b** 16%.[25] The discrepancy between the formation of (+)-litsenolide D_2 (*trans*,*E*-**2b**) from *cis*,*E*-**1b** and AD-mix α™ and Sharpless' mnemonic guideline for the side-selectivity of this reaction should be noted.[3] By their ^{1}H NMR spectra and the signs of their specific rotations, lactones *ent*-*trans*,*Z*-**2b** (levorotatory) and *trans*,*E*-**2b** (dextrorotatory) were identical with natural (−)-litsenolide D_1 and the mirror image of natural (−)-litsenolide D_2, respectively. These compounds were thus prepared in non-racemic form for the first time, the straightforwardness of our three-step route being attractive in view of step-requirements between 8 and 13 of the previous syntheses.[26]

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