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A VERSATILE STEREOSELECTIVE APPROACH TO PARACONIC ACIDS

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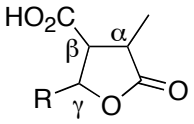
Abstract – A versatile methodology has been developed for the independent stereochemical control in the construction of all the stereocenters of the γ-butyrolactone skeleton that are present in paraconic acids (**1** and **2**). The configuration of the γ-carbon came from an enantiopure alk-2-yne-1,4-diol. Stereoselective partial reduction to a (*Z*)- or (*E*)-alk-2-ene-1,4-diol (**10**) controlled the stereochemistry of the β-carbon whereas the α-carbon stereochemistry in **1** was partially selected by a (*Z*)- or (*E*)-enolate formation of the 1,4-dipropanoate derived from diol (**10**).

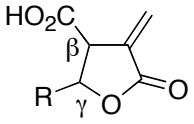
INTRODUCTION†

Paraconic acids (**1** or **2** in Figure 1) are a variety of naturally occurring trisubstituted γ-butyrolactones isolated from various species of fungi, lichens and moses.[1] These lactones display a broad biological profile that includes antifungal, antitumor and antibacterial activities.[2] Their common framework is a γ-butyrolactone that possess a very similar substitution pattern at the α-position (methyl or methylene group) and β-position (carboxyl group). However, the main differences within the family are found in the group at γ-position (usually an alkyl chain) as well as the stereochemical relationship between these substituents. Examples of compounds with *trans* relationships between the β and γ substituents are roccellaric acid[3] (**3**) and nephrosteranic acid[4] (**4**), both with a methyl at the α position; and also α methylene lactones like protolichesterinic acid[5] (**5**) or methylenolactocin[6] (**6**). However, *cis* β,γ-substituted compounds like nephromopsinic acid[7] (**7**) or phaseolinic acid[8] (**8**) can be also found. Due to their biological significance many stereoselective synthetic methods have been developed to obtain either these *trans*-[9] or *cis*-[10] β,γ-substituted γ-butyrolactones.

† This paper is dedicated to Professor Barry M. Trost on the occasion of his 65th birthay.



1



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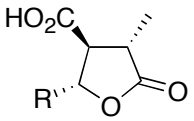
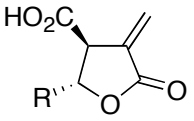
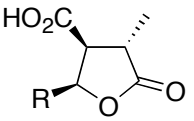


R = $C_{13}H_{27}$
(+)-Roccellaric acid (**3**)
R = $C_{11}H_{23}$
(+)-Nephrosteranic acid (**4**)



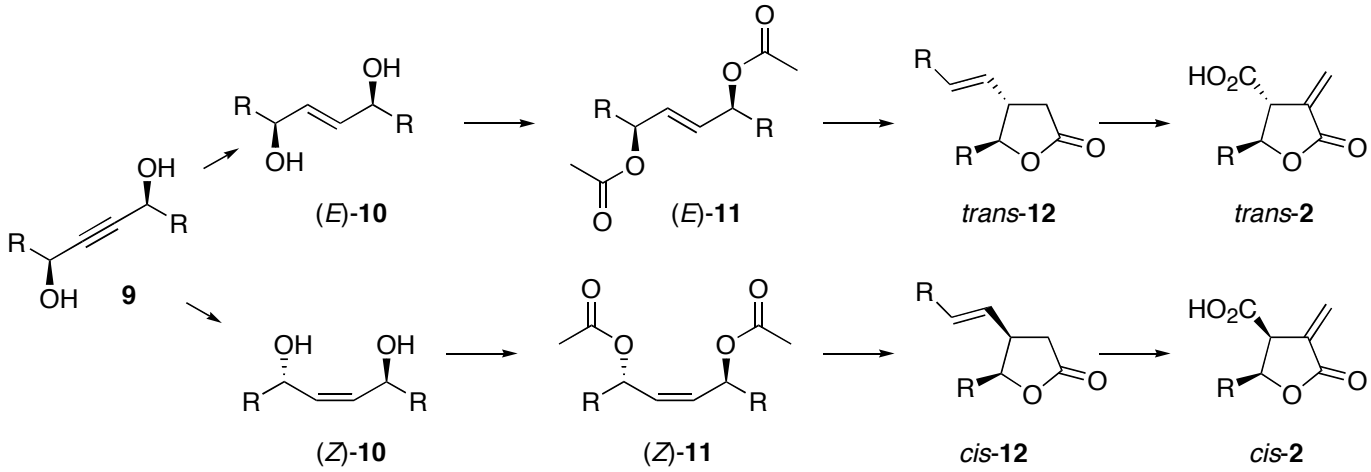
R = $C_{13}H_{27}$
(+)-Protolichesterinic acid (**5**)
R = C_5H_{11}
(+)-Methylenolactocin (**6**)



R = $C_{13}H_{27}$
(–)-Nephromopsinic acid (**7**)
R = C_5H_{11}
(–)-Phaseolinic acid (**8**)

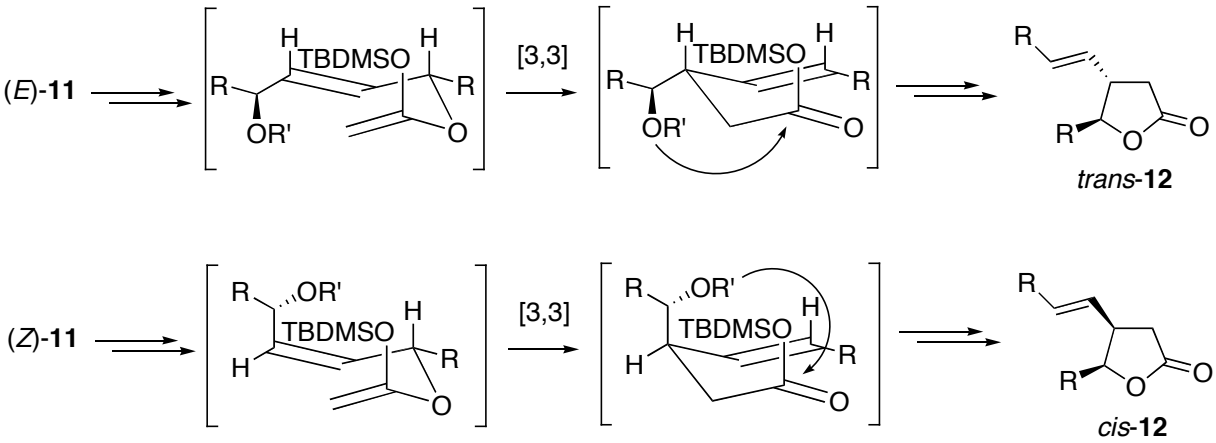
Figure 1

Our group has been interested in developing a stereodivergent approach that allowed an access to all the possible stereoisomers of such lactones, and therefore, the preparation of both *trans*- or *cis*- β,γ-substituted paraconic acids (**2**) from a common precursor.[11] Thus, the chiral enantioenriched C_2-symmetrical alk-2-yne-1,4-diol (**9** in Scheme 1) could be easily transformed by a selective partial reduction of the triple bond into either (*E*)-**10** or (*Z*)-**10**. These diols would eventually afford lactones *trans*-**2** or *cis*-**2**, respectively.



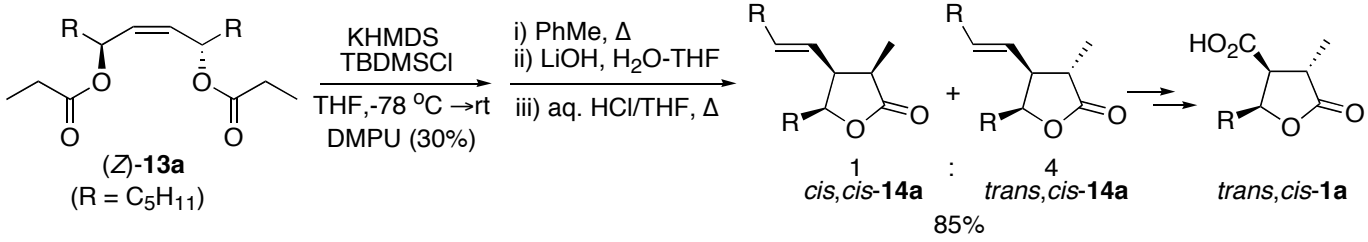
Scheme 1

The key step in this approach was the transformation of **11** to **12** by a [3,3] sigmatropic rearrangement (Scheme 2). In this process the stereochemical information was transferred in a cyclic transition state by an Ireland-Claisen rearrangement[12] of the *tert*-butyldimethylsilyl enolates derived from diacetates (**11**). Hydrolysis of the rearranged product and further cyclization afforded the lactones (**12**) that could be easily transformed into **2** by an oxidative cleavage of the double bond and methylenation by a known procedure.[13] Actually, this methodology was used for the stereoselective synthesis of the lactones *trans*-**12a** (R = C_5H_{11}) and *cis*-**12a** (R = C_5H_{11}) as precursors of methylenolactocin and phaseolinic acid.[11]



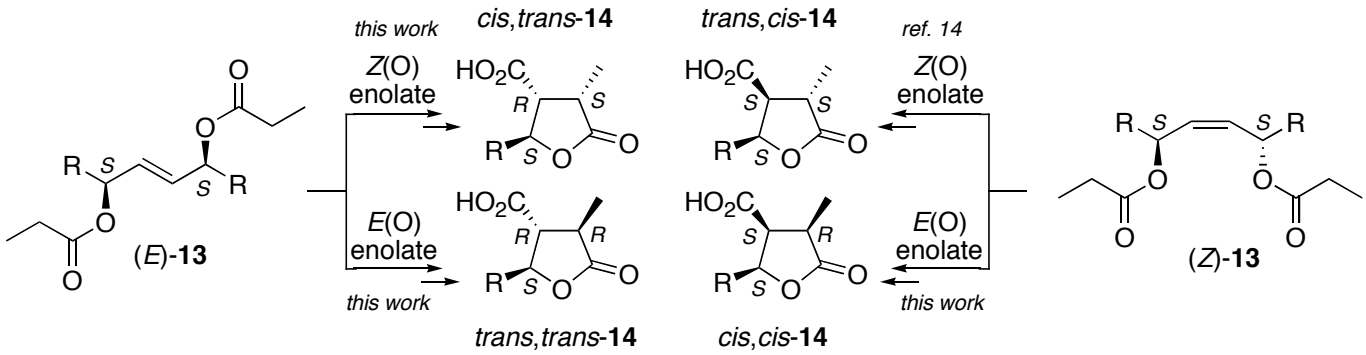
Scheme 2

Having in hand a procedure for the synthesis of methylene lactones (**2**), we focused our efforts on the control of the α–stereocenter of methyl lactones (**1**). Obviously, the rearrangement of the dipropanoate derivative of **10** would afford an α–methylated product. We envisaged that the control of the stereochemistry could come from a selective enolization prior to the rearrangement step. As expected, when we enolized the *cis*-dipropanoate ((*Z*)-**13a**) with KHMDS and TBDMSCl in a 30% mixture of DMPU/THF we obtained after rearrangement and cyclization a crude mixture where the α,β-*trans*, β,γ-*cis* lactone (*trans*,*cis*-**14a**) predominated over the minor *cis*,*cis* isomer (ratio 4:1). Isolation of *trans*,*cis*-**14a** followed by further transformations gave phaseolinic acid (*trans*,*cis*-**1a**) as a single isomer (Scheme 3).[14]



Scheme 3

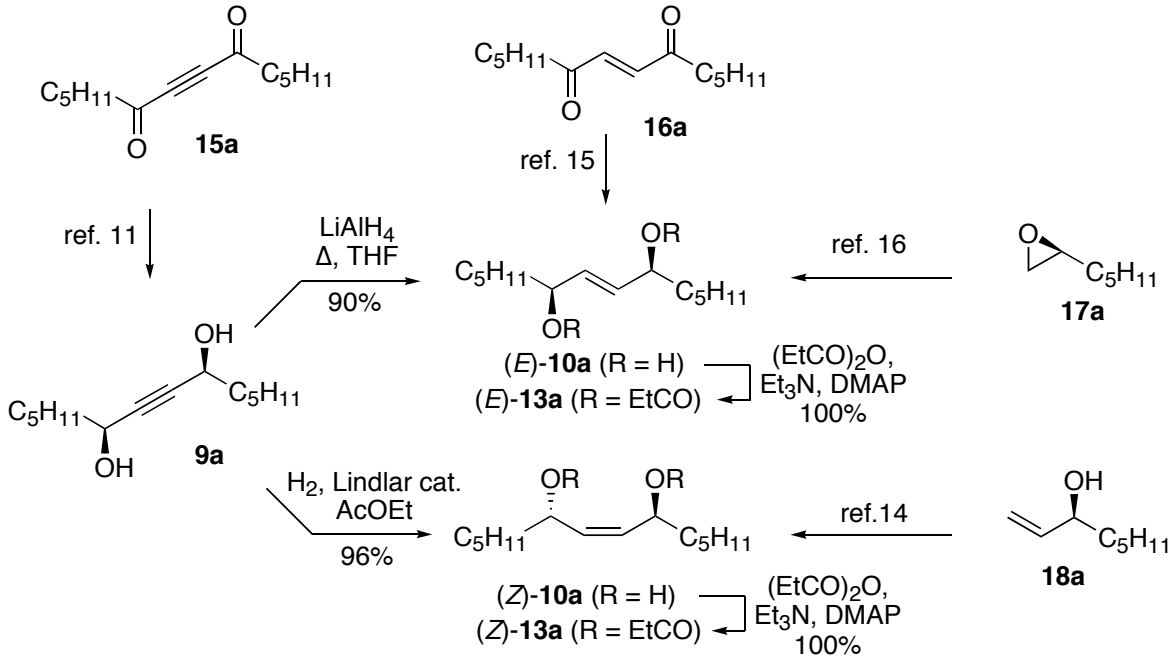
According to the enolization conditions, this rearrangement should go through the *Z*(O)-*tert*-butyldimethylsilyl enolate.[12] On the other hand, we expected that enolization conditions leading to the *E*(O)-*tert*-butyldimethylsilyl enolate should give the *cis*,*cis*-**14** as a major stereoisomer. In this paper we explore this assumption. Eventually, we could prepare all the possible relative stereochemistries of **1** from a single chiral alk-2-yne-1,4-diol (Scheme 4). Therefore, the stereochemistry of the α methyl would be selected by the appropriate enolization conditions to obtain the suitable enolate (*Z* or *E*), the stereochemistry of the β carbon would be selected by the configuration of the double bond, whereas the configuration of the γ position would determined by the stereochemistry of the starting alk-2-yne-1,4-diol.



Scheme 4

RESULTS AND DISCUSSION

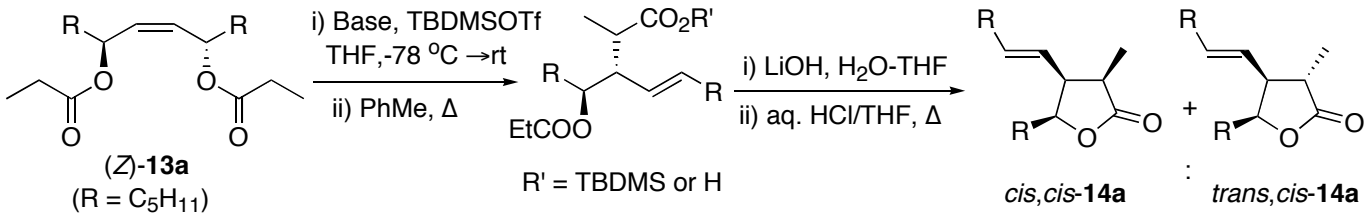
As a C_2-symmetrical alk-2-yne-1,4-diol we chose tetradec-7-yne-6,9-diol (**9a**). This alkyne can be prepared by stereoselective reduction of the corresponding diketone (**15a**) and it can be reduced selectively either to olefin ((*E*)-**10a**) with $LiAlH_4$ or ((*Z*)-**10a**) by hydrogenation.[11] Alternatively (*E*)-**10a** can be also prepared by reduction of the diketone (**16a**)[15] or in a straightforward manner by a reported coupling of a terminal epoxide (**17a**).[16] On the other hand, (*Z*)-**10a** can be also prepared by metathesis of 1-octen-3-ol (**18a**)[14] (Scheme 5). Each alk-2-ene-1,4-diol can be easily transformed in the corresponding dipropanoate ((*E*)-**13a** and (*Z*)-**13a**) by a standard procedure.



Scheme 5

The analysis of the enolization-rearrangement step was initially studied for (*Z*)-**13a**. Ireland *et al.* described that *Z*(O)-silyl enolates of esters can be obtained with an amide as a base when HMPA or DMPU is used.[12] In contrast, the *E*(O)-silyl enolate predominated in absence of DMPU. Actually, after an

optimization process, we were able to obtain the *cis*,*cis* lactone (*cis*,*cis*-**14a**) as a major product by using LDA as a base (Scheme 6).

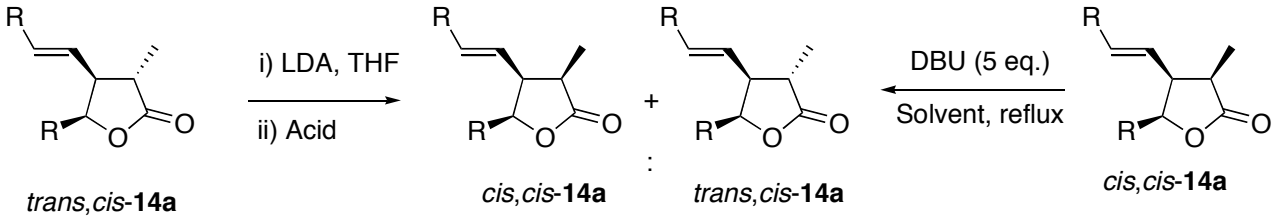


LHMDS	2.75 : 1	48%
KHMDS	4.60 : 1	42%
LDA	**5.80 : 1**	**65%**

Scheme 6

Since both isomers of **14a** are separable chromatographically, it was possible to improve the overall yield of *cis*,*cis*-**14a** by conversion of the minor isomer (*trans*,*cis*-**14a**) into the major (*cis*,*cis*-**14a**) *via* a kinetic protonation of the corresponding lithium enolate (Scheme 7).[17] Thus, the enolization of *trans*,*cis*-**14a** with LDA and protonation with several weak acids afforded the *cis*,*cis*-**14a** as a major isomer. Among them, ethyl salicylate gave the best result in our hands.[18]

Alternatively, the minor isomer coming from a *Z*(O)-enolization (i.e. *cis*,*cis*-**14a**) can be converted into the *trans*,*cis*-**14a** isomer under thermodynamic equilibration. Thus, pure lactone (*cis*,*cis*-**14a**) was converted into a mixture of *trans*,*cis* and *cis*,*cis* isomers by heating with 5 eq. of DBU in several solvents. In all the cases the final ratio was close to 70:30 in favor of *trans*,*cis*-**14a**.



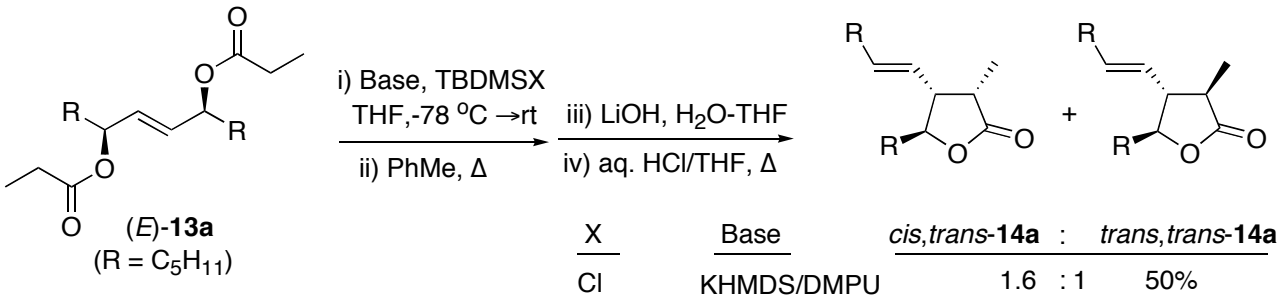
Acid	*cis,cis* : *trans,cis*
ethyl salicylate	**4.64 : 1**
aq. Na_2SO_4 sat.	3.23 : 1
ethyl acetoacetate	1.10 : 1

Solvent	*cis,cis* : *trans,cis*
none	**30 : 70**
pyridine	31 : 69
MeCN	32 : 68
heptane	33 : 67
toluene	34 : 66

Scheme 7

Since any kind of epimerization was not observed in the transformation of *cis*,*cis*-**14a** and *trans*,*cis*-**14a** into **1a**,[14] at this point we were able to prepare with good overall yield and selectivity two of the four diasteroisomers of **1a**. Our next step was to examine the enolization-rearrangement tandem on the *E*-

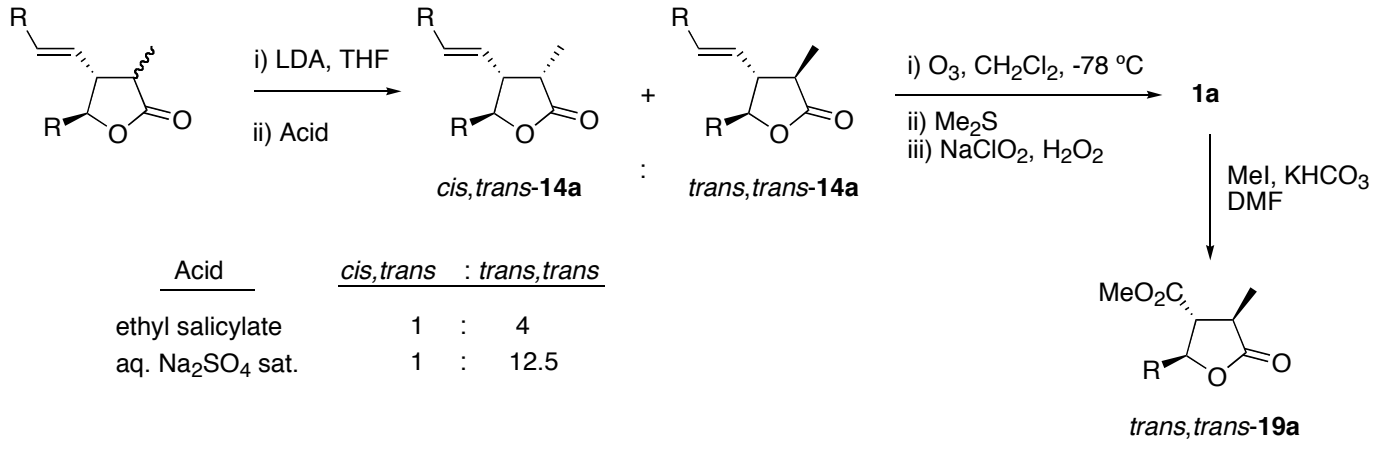
alkene ((*E*)-**13a**). Initially our efforts were directed to the formation of a *Z*(O)-silyl enolate. After optimization, the best conditions were again by using KHMDS, TBDMSCl in the presence of DMPU (40%). Although under these conditions the expected *cis*,*trans*-**14a** was obtained as the major isomer, only a modest selectivity (ratio *cis*,*trans*-**14a**/*trans*,*trans*-**14a**: 1.6:1) was observed.[19] The selectivity could be reversed in the absence of DMPU. In this case the major isomer was the *trans*,*trans*-**14a** (ratio *trans*,*trans*-**14a**/*cis*,*trans*-**14a**: 1.5:1). The use of LDA as base and TBDMSOTf did not improve the ratio (Scheme 8).



X	Base	*cis*,*trans*-**14a** :	*trans*,*trans*-**14a**
Cl	KHMDS/DMPU	1.6 : 1	50%
Cl	KHMDS	1 : 1.5	70%
OTf	LDA	1 : 1.2	62%

Scheme 8

Considering the low selectivities obtained, we tried to improve the ratio by kinetic protonation or thermodynamic equilibration (Scheme 9). To our satisfaction, the kinetic protonation of the lithium enolate of **14a** afforded stereoselectively the *trans*,*trans* isomer (ratio *trans*,*trans*-**14a**/*cis*,*trans*-**14a**: 12.5:1), being in this case a saturated aqueous solution of Na_2SO_4 the best quencher.[20] Unfortunately, thermodynamic equilibration with DBU in refluxing toluene led to the same major *trans*,*trans* isomer in the equilibrium mixture (ratio 9:1).

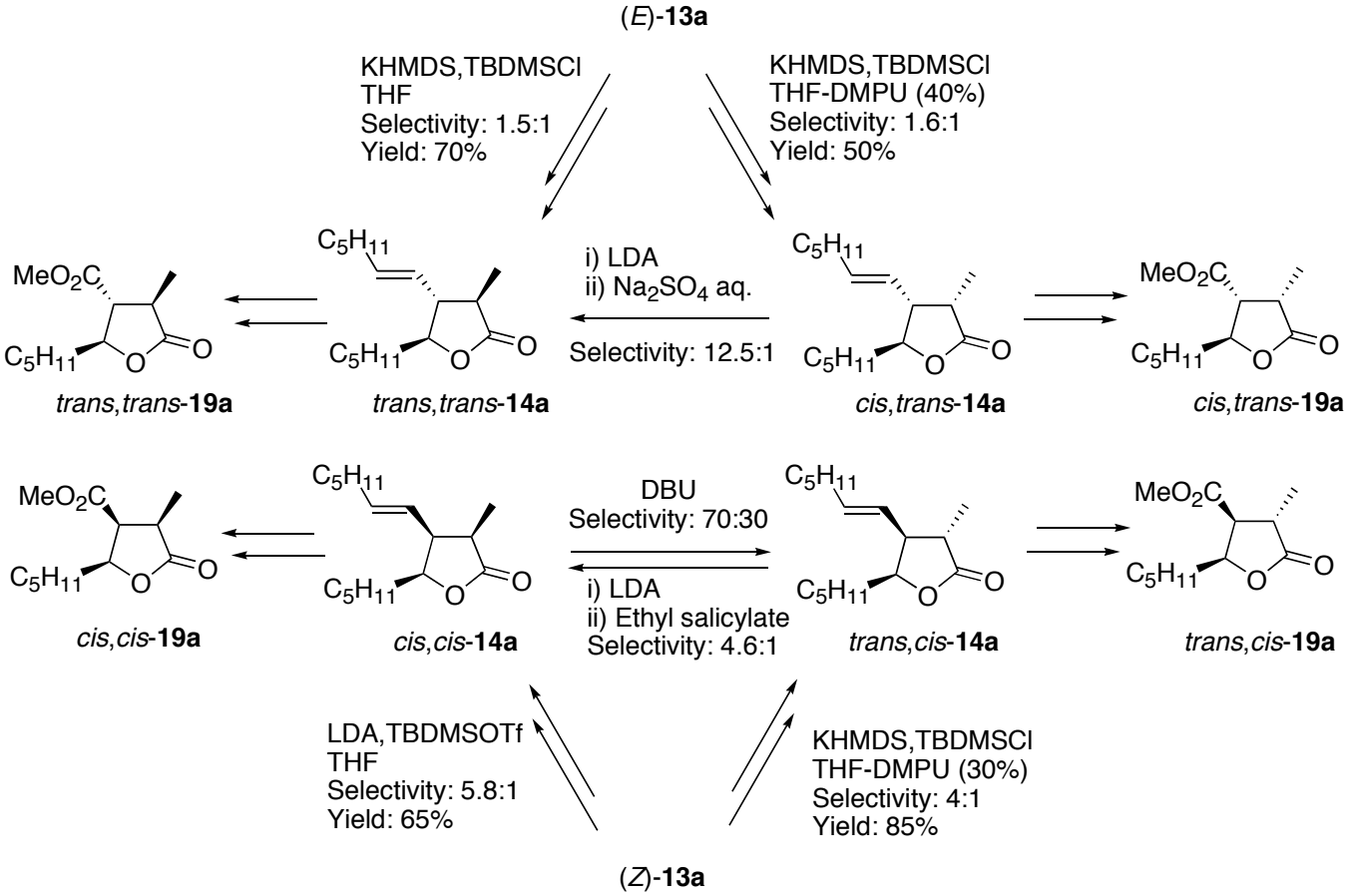


Acid	*cis*,*trans* :	*trans*,*trans*
ethyl salicylate	1 :	4
aq. Na_2SO_4 sat.	1 :	12.5

Scheme 9

The inseparable mixture of **14a** was transformed directly to the corresponding paraconic acid **1a** without any loss of stereochemical integrity (Scheme 9). Finally, the minor isomer was removed by converting the mixture of acids (*trans*,*trans*-**1a**) and (*cis*,*trans*-**1a**) into their methyl esters (**19a**) that could be separated. In order to obtain the four diastereomers of methyl esters (**19a**) and compare their spectra, samples of acids (*trans*,*cis*-**1a**) and (*cis*,*cis*-**1a**) were also converted into their corresponding methyl esters (i.e. *trans*,*cis*-**19a** and *cis*,*cis*-**19a**).[21]

In summary, we were able to prepare all four diastereomers of **1a** and their methyl esters (**19a**) from a common chiral starting diol (**9a**). The key step was a stereoselective [3,3] sigmatropic Ireland-Claisen rearrangement of the (O)-*tert*-butyldimethylsilyl enolates of **13a**. Complete control of the transfer of chirality at ß-carbon was obtained in such processes. High stereoselectivities at the α carbon were noted when the dipropanoate ((*Z*)-**13a**) was used through its corresponding *Z*(O)- or *E*(O)-enolate. However, only modest selectivities were obtained with (*E*)-**13a** as a substrate. Nevertheless, the obtained ratios of epimers of **14a** at the α carbon were improved by kinetic protonation of the corresponding lithium enolates and/or thermodynamic isomerization (Scheme 10).



Scheme 10

EXPERIMENTAL

All the solvents were distilled from an appropriate drying agent and stored under nitrogen atmosphere. The crude products were separated by column chromatography on silica gel of 230-400 mesh (flash chromatography). TLC was performed on HF_{254} silica gel plates. Chemical shifts are given in ppm with respect to internal TMS. IR spectra were measured on a Perkin-Elmer 681 on NaCl plates (neat) or in KBr; only the most significant absorptions, in cm^{-1}, are indicated. Microanalyses were performed by the Serveis Científico-Tècnics (Universitat de Barcelona). Optical rotations were measured at 20 ± 2 ºC. HRMS (EI) spectra were obtained at the CACTI (Universidad de Vigo). Compounds (**9a**),[22] ((*E*)-**10a**),[22] and ((*Z*)-**13a**)[14] were prepared according to published procedures.

(*6S*,7*Z*,9*S*)-Tetradec-7-ene-6,9-diol [(*Z*)-10a]:

Quinoline (26 μL, 0.22 mmol) and Pd/$CaCO_3$ (5% Pd, 113 mg, 0.053 mmol) were added to a solution of diol (**9a**) (800 mg, 3.53 mmol) in AcOEt (20 mL) under nitrogen. H_2 was bubbled through the mixture for a few minutes. Then, the mixture was kept under H_2 pressure (1 atm) and shaked vigorously for 1 h. The mixture was filtered through a small pad of Celite®. Additional AcOEt was added to wash the pad. The solvent was evaporated under vacuum and the residue was purified by flash chromatography (98:2 hexane/AcOEt) to give (*Z*)-**10a** (771 mg, 96%) as a colorless oil: $\mathbf{R_f}$ = 0.5 (65:35 hexane/AcOEt); $[\alpha]_D$ –2.6º (*c* 1.1, $CHCl_3$) for (6*S*,7*Z*,9*S*)-**10a**; **IR** (film) 3361, 2958, 2931, 1468; **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 0.89 (t, *J* = 6.6, 6H), 1.30-1.52 (m, 14H), 1.85 (bs, 2H), 4.44 (td, *J* = 6.0, 2.0, 2H), 5.48 (m, 2H); **^{13}C NMR** ($CDCl_3$, 100.6 MHz) δ 14.0, 22.6, 25.1, 31.7, 37.6, 68.3, 134.3; **HRMS** (EI) calcd for $C_{14}H_{28}O_2$ $[M]^+$ 228.2089, found 228.2088. Anal. Calcd for $C_{14}H_{28}O_2$: C, 73.63; H, 12.36. Found C, 73.42; H 12.38.

(*E*)-1-Pentyl-4-propanoyloxynon-2-enyl propanoate [(*E*)-13a]:

Triethylamine (439 μL, 3.15 mmol) was added to a solution of (*E*)-**10a** (240 mg, 1.05 mmol) and DMAP (13 mg, 0.11 mmol) in CH_2Cl_2 (5 mL). The solution was cooled to 0 ºC and propanoic anhydride (406 μL, 3.15 mmol) was added dropwise. The mixture was stirred at rt overnight. Then, the solution was diluted with CH_2Cl_2 (3 mL), washed with saturated aq. $NaHCO_3$ (4 mL) and with phosphate buffer (pH = 7, 4 mL). The organic layer was dried over $MgSO_4$. The solvent was evaporated under vacuum and the residue was purified by flash chromatography (98:2 CH_2Cl_2/MeOH) to give (*E*)-**13a** (358 mg, 100%) as a colorless oil: $\mathbf{R_f}$ = 0.22 (1:1 hexane/CH_2Cl_2) or 0.56 (9:1 hexane/AcOEt); **IR** (film): 2934, 1733, 1654, 1123; **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 0.88 (t, *J* = 7.2, 6H), 1.14 (t, *J* = 7.6, 6H), 1.27 (m, 12H), 1.53-1.65 (m, 4H), 2.32 (q, *J* = 7.6, 4H), 5.24 (m, 2H), 5.61 (m, 2H); **^{13}C NMR** ($CDCl_3$, 100.6 MHz): δ 9.1, 13.9, 22.5, 24.6, 27.8, 31.4, 34.3, 73.5, 130.9, 173.6; **HRMS** (EI) calcd for $C_{20}H_{36}O_4$ $[M]^+$ 340.2614, found 340.2621; Anal. Calcd for $C_{20}H_{36}O_4$: C 70.55; H 10.66. Found C 70.60, H 10.99.

Enolization and rearrangement of dipropanoates (*Z*)-13a:

General procedure: Dipropanoate (*Z*)-**13a** (100 mg, 0.29 mmol) was dissolved in anhydrous THF (2.5 mL). TBDMSOTf (269 μL, 1.17 mmol) was added and the reaction mixture was cooled at –78 ºC. The base was added dropwise (0.87 mmol) and the mixture was stirred for 45 min, then it was warmed to rt for 4 h. The solvent was removed under vacuum, dry toluene (3 mL) was added and the mixture was heated to reflux until the starting material was consumed as determined by TLC analysis (typically 16 h). The mixture was dissolved in Et_2O (8 mL) and washed with aqueous saturated NH_4Cl (5 mL). The aqueous layer was extracted with Et_2O, the combined organic layer was dried over $MgSO_4$ and the solvent was removed under vacuum. The crude mixture was dissolved in THF (2 mL) and LiOH 6 M (1 mL) and it was heated for 20 h at 70 ºC. The solution was acidified with HCl 2 M (6 mL), THF (3 mL) was added and the mixture was heated at 50 ºC for 2 h. The reaction can be monitored by TLC (9:1 hexane/AcOEt). The mixture was diluted with CH_2Cl_2 (10 mL), the organic layer was separated and dried over $MgSO_4$. The solvent was evaporated under vacuum and purified by column chromatography (9:1 hexane/AcOEt).

With LHMDS: LHMDS 1 M in THF (870 μL) afforded *cis*,*cis*-**14a** (27 mg) and *trans*,*cis*-**14a** (10 mg).

With KHMDS: KHMDS 0.5 M in toluene (1.74 mL) afforded *cis*,*cis*-**14a** (25 mg) and *trans*,*cis*-**14a** (6 mg).

With LDA: Commercial LDA 1.8 M in heptane (483 μL) afforded *cis*,*cis*-**14a** (43 mg) and *trans*,*cis*-**14a** (7 mg).

Compound *cis*,*cis*-**14a:** colorless oil; $\mathbf{R_f}$ = 0.41 (9:1 hexane/AcOEt); $\mathbf{[\alpha]_D}$ –37.7º (*c* 1.03, $CHCl_3$) for (3*R*,4*S*,5*S*)-**14a**; **IR** (film): 2958, 2931, 2860, 1777, 1457, 1175; **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 0.88 (t, *J* = 6.8, 6H), 1.08 (d, *J* = 7.2, 3H), 1.22-1.50 (m, 12H), 1.62-1.68 (m, 2H), 2.06 (m, 2H), 2.79 (dq, *J* = 7.2, 7.2, 1H), 2.90 (m, 1H), 4.32 (dt, *J* = 7.2, 5.2, 1H), 5.13 (dd, *J* = 15.2, 10.8, 1H), 5.54 (dt, *J* = 15.2, 7.2, 1H); **^{13}C NMR** ($CDCl_3$, 100.6 MHz): δ 10.7, 13.9, 14.0, 22.4, 22.5, 25.0, 28.9, 30.8, 31.2, 31.6, 32.4, 40.3, 48.5, 82.0, 122.5, 136.4, 179.2; **HRMS** (EI) calcd for $C_{17}H_{30}O_2$ $[M]^+$ 266.2246, found 266.2247; Anal. Calcd for $C_{17}H_{30}O_2$: C 76.64, H 11.35. Found C 76.40, H 11.25.

Compound *trans*,*cis*-**14a:** colorless oil; $\mathbf{R_f}$ = 0.59 (9:1 hexane/AcOEt); $\mathbf{[\alpha]_D}$ –75.3º (*c* 1.57, $CHCl_3$) for (3*S*,4*S*,5*S*)-**14a**; **IR** (film): 2931, 2860, 1777, 1459, 1171; **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 0.87-0.93 (m, 6H), 1.19 (d, *J* = 7.2, 3H), 1.24-1.41 (m, 12H), 1.46-1.56 (m, 2H), 2.05 (m, 2H), 2.43 (dq, *J* = 10.8, 7.2, 1H), 2.74 (m, 1H), 4.45 (m, 1H), 5.32 (ddt, *J* = 15.2, 9.0, 1.2, 1H), 5.58 (dt, *J* = 15.2, 6.8, 1H); **^{13}C NMR** ($CDCl_3$, 100.6 MHz): δ 13.4, 13.9, 14.0, 22.4, 22.5, 25.5, 28.9, 30.8, 31.3, 31.6, 32.5, 38.8, 50.5, 81.4, 125.4, 135.5, 179.1; **HRMS** (EI) calcd for $C_{17}H_{30}O_2$ $[M]^+$ 266.2246, found 266.2241; Anal. Calcd for $C_{17}H_{30}O_2$: C 76.64, H 11.35. Found C 76.82, H 11.21.

Isomerization of *trans*,*cis*-14a by kinetic protonation of enolates:

General procedure: A solution of commercial LDA (1.8 M in heptane, 75 μL, 0.14 mmol) was added to a mixture of 24 mg (0.09 mmol) of lactones *cis*,*cis*-**14a** and *trans*,*cis*-**14a** in dry THF (1 mL) at –78 ºC. The mixture was stirred for 5 min and warmed to 0 ºC for 30 min before cooling it again to –78 ºC. This solution was added *via* cannula to a solution of the acid in THF (1 mL) at –78 ºC. The mixture was warmed to rt, CH_2Cl_2 was added and washed with water. The combined organic layer was dried over $MgSO_4$ and the solvent was removed under vacuum.

With ethyl salicylate as acid: Ethyl salicylate (38 μL, 0.23 mmol) afforded a mixture of *cis*,*cis*-**14a** and *trans*,*cis*-**14a** in a 4.64:1 ratio.

With aqueous Na_2SO_4 as acid: Saturated aqueous Na_2SO_4 (300 μL) afforded a mixture of *cis*,*cis*-**14a** and *trans*,*cis*-**14a** in a 3.23:1 ratio.

Thermodynamic equilibration of *cis*,*cis*-14a:

A solution of 10 mg (0.038 mmol) of lactone (*cis*,*cis*-**14a**) and DBU (45 μL, 0.19 mmol) in the appropriate solvent (1 mL or without solvent) was heated to reflux. The reaction was monitored by TLC until no further changes were observed (~ 42 h). The mixture was acidified with HCl 2 N and extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$ and the solvent was removed under vacuum. The ratio of isomers was analyzed by ^{1}H NMR spectrum of the crude mixture. In all cases the ratio of *cis*,*cis*-**14a**/*trans*,*cis*-**14a** was ~3:7.

Enolization and rearrangement of dipropanoates ((*E*)-13a):

General procedure: Dipropanoate ((*E*)-**13a**) (100 mg, 0.29 mmol) was dissolved in dry THF (3 mL) and DMPU (1.4 mL) when needed. The silylating agent (1.17 mmol) was added and the reaction mixture was cooled to –78 ºC. The base was added dropwise (0.87 mmol) and the mixture was stirred for 45 min, then it was warmed to rt overnight. The solvent was removed under vacuum, dry toluene (3 mL) was added and the mixture was heated to reflux until the starting material was consumed as determined by TLC analysis (typically 16 h). The mixture was dissolved in Et_2O (8 mL) and washed with aqueous saturated NH_4Cl (5 mL). The aqueous layer was extracted with Et_2O, the combined organic layer was dried over $MgSO_4$ and the solvent was removed under vacuum. The crude mixture was dissolved in THF (2 mL) and LiOH 6 M (1 mL) and it was heated for 16 h at 70 ºC. The solution was acidified with HCl 2 M (6 mL), THF (3 mL) was added and the mixture was heated at 50 ºC for 2 h. The reaction can be monitored by TLC (9:1 hexane/AcOEt). The mixture was diluted with CH_2Cl_2 (10 mL), the aqueous layer was extracted twice with CH_2Cl_2 (2 x 5 mL) and the combined organic layer was separated and dried over $MgSO_4$. The

solvent was evaporated under vacuum and purified by column chromatography (9:1 hexane/AcOEt) to give a mixture of *cis*,*trans*-**14a** and *trans*,*trans*-**14a** as a colorless oil (R_f = 0.38).

With KHMDS without DMPU: Silylating agent (TBDMSCl, 176 mg) and base (KHMDS 0.5 M in toluene, 1.74 mL) afforded 55 mg (ratio *cis*,*trans*/*trans*,*trans*: 1:1.5).

With LDA without DMPU: Silylating agent (TBDMSOTf, 269 μL) and base (commercial LDA 1.8 M in heptane, 1.74 mL) afforded 48 mg (ratio *cis*,*trans*/*trans*,*trans*: 1:1.2).

With KHMDS and DMPU: Silylating agent (TBDMSCl, 176 mg) and base (KHMDS 0.5 M in toluene, 1.74 mL) afforded 39 mg (ratio *cis*,*trans*/*trans*,*trans*: 1.6:1). Data for the major isomer *cis*,*trans*-**14a**: $\mathbf{R_f}$ = 0.38 (9:1 hexane/AcOEt); **IR** (film): 2957, 2930, 2859, 1778, 1173; **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 0.89 (t, *J* = 6.8, 6H), 1.16 (d, *J* = 7.2, 3H), 1.26-1.40 (m, 11H), 1.51-1.63 (m, 3H), 2.04 (qd, *J* = 7.2, 0.8, 2H), 2.73 (m, 2H), 4.20 (ddd, *J* = 8.0, 6.4, 4.8, 1H), 5.28 (ddt, *J* = 15.2, 8.8, 0.8, 1H), 5.56 (dt, *J* = 15.2, 7.2, 1H); **^{13}C NMR** ($CDCl_3$, 100.6 MHz): δ 11.4, 13.9, 14.0, 22.4, 22.4, 25.4, 28.8, 31.3, 31.5, 32.5, 33.6, 39.0, 48.6, 83.3, 125.0, 135.6, 179.7; **HRMS** (EI) calcd for $C_{17}H_{30}O_2$ $[M]^+$ 266.2246, found 266.2242.

Isomerization of a mixture of *trans*,*trans*-14a and *cis*,*trans*-14a by kinetic protonation of enolates:

General procedure: A solution of commercial LDA (1.8 M in heptane, 47 μL, 0.08 mmol) was added to a mixture of 15 mg (0.06 mmol) of lactones (*trans*,*trans*-**14a**) and (*cis*,*trans*-**14a**) (in a 1:1.3 ratio) in dry THF (1 mL) at –78 ºC. The mixture was stirred for 5 min and warmed to 0 ºC for 30 min before cooling it again to –78 ºC. This solution was added via cannula to the acid in THF (1 mL) at –78 ºC. The mixture was warmed to rt, CH_2Cl_2 was added and washed with water. The combined organic layer was dried over $MgSO_4$ and the solvent was removed under vacuum.

With ethyl salicylate as acid: Ethyl salicylate (38 μL, 0.23 mmol) afforded a mixture of *trans*,*trans*-**14a** and *cis*,*trans*-**14a** in a 4:1 ratio.

With aqueous Na_2SO_4 as acid: Saturated aqueous Na_2SO_4 (300 μL) and a couple of drops of saturated aqueous $NaHSO_4$ afforded a mixture of *trans*,*trans*-**14a** and *cis*,*trans*-**14a** in a 12.5:1 ratio as a colorless oil. Data for the major isomer *trans*,*trans*-**14a**: $\mathbf{R_f}$ = 0.38 (hexane/AcOEt 9:1); **IR** (film): 2958, 2930, 2858, 1779, 1172; **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 0.89 (t, *J* = 6.8, 6H), 1.18 (d, *J* = 6.8, 3H), 1.26-1.41 (m, 11H), 1.46-1.56 (m, 2H), 1.66-1.69 (m, 1H), 2.04 (qd, *J* = 6.8, 2.8, 2H), 2.22 (dt, *J* = 11.6, 8.8, 1H), 2.38 (dq, *J* = 11.6, 7.0, 1H), 4.01 (td, *J* = 8.4, 3.6, 1H), 5.23 (ddt, *J* = 15.2, 8.6, 1.6, 1H), 5.60 (dt, *J* = 15.2, 7.0, 1H); **^{13}C NMR** ($CDCl_3$, 50.3 MHz): δ 12.8, 14.0, 14.1, 22.5, 22.5, 25.5, 28.9, 31.3, 31.6, 32.5, 33.3, 42.0, 54.5, 82.9, 126.5, 135.8, 178.5; **HRMS** (EI) calcd for $C_{17}H_{30}O_2$ $[M]^+$ 266.2246, found 266.2247.

Thermodynamic equilibration of a mixture of *trans*,*trans*-14a and *cis*,*trans*-14a:

A solution of 10 mg (0.038 mmol) of lactones (*trans*,*trans*-**14a**) and (*cis*,*trans*-**14a**) (1:1.3 ratio) and DBU (45 μL, 0.19 mmol) in toluene (2 mL) was heated to reflux. The reaction was monitored by TLC until no further changes were observed (~ 48 h). The mixture was acidified with HCl 2 N and extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$ and the solvent was removed under vacuum. The ratio was analyzed by ^{1}H NMR of the crude mixture. The final observed ratio of *trans*,*trans*-**14a** and *cis*,*trans*-**14a** was 9:1.

Transformation of lactones (14a) into acids (1a):

Acid (*trans*,*trans*-1a): Ozone was bubbled through a solution of lactone (*trans*,*trans*-**14a**) (55 mg, 0.21 mmol, 10:1 ratio with *cis*,*trans*-**14a**) in dry CH_2Cl_2 (6 mL) at –78 ºC. Once the starting lactone disappeared (as shown by TLC, 9:1 hexane/AcOEt) ozone was replaced by nitrogen for some minutes. Then, Me_2S (60 μL) was added and the mixture was stirred at rt for 90 min. The mixture was diluted with CH_2Cl_2 (5 mL) and was washed with phosphate buffer (pH = 7, 6 mL). The organic layer was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layer was dried over anhydrous $MgSO_4$ and the solvent was removed under vacuum. The crude mixture (41 mg) was mainly the aldehyde that was used without further purification. Thus, the crude was dissolved in MeCN (1.5 mL). A solution of NaH_2PO_4 (23 mg) in water (0.9 mL), H_2O_2 (0.24 mL) and $NaClO_2$ (39 mg, 0.43 mmol) were added. When the starting material was consumed (as shown by TLC, 65:35 hexane/AcOEt), the reaction was quenched with a solution of $NaHSO_3$ (51 mg) in water (0.8 mL) for 30 min. The mixture was basified with NaOH 1 M and extracted with AcOEt (8 mL). The aqueous layer was acidified with HCl 2 M and was extracted with AcOEt (6 x 10 mL). The combined organic layer was dried over $MgSO_4$ and the solvent was removed under vacuum. The crude mixture was not further purified and the acid (*trans*,*trans*-**1a**) was obtained in 64% yield (28 mg) as a colorless solid: **mp** 84-86 ºC (AcOEt); **IR** (KBr): 3352, 2928, 2859, 1780, 1744, 1712, 1175; **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 0.90 (t, *J* = 6.8, 3H), 1.28-1.44 (m, 5H), 1.37 (d, *J* = 7.2, 3H), 1.51-1.54 (m, 1H), 1.71 (m, 1H), 1.82 (m, 1H), 2.70 (dd, *J* = 11.2, 9.2, 1H), 2.99 (dq, *J* = 11.2, 7.2, 1H), 4.48 (ddd, *J* = 9.2, 8.2, 4.0, 1H), 9.33 (br s, 1H, OH); **^{13}C NMR** ($CDCl_3$, 100.6 MHz): δ 13.9, 14.5, 22.4, 24.9, 31.3, 34.9, 39.8, 53.9, 79.3, 175.8, 176.6. **HRMS** (EI) calcd for $C_{11}H_{18}O_4$ $[M]^+$ 214.1205, found 214.1197.

Acid (*cis*,*trans*-1a): A similar procedure as for *trans*,*trans*-**1a** was carried out . Thus, a mixture of lactones (*trans*,*trans*-**14a**) and (*cis*,*trans*-**14a**) (50 mg, 1:1 ratio) afforded a mixture of acid (*trans*,*trans*-**1a**) and (*cis*,*trans*-**1a**) (33 mg, 0.95:1 ratio) in a 84% overall yield as a colorless oil. Data for *cis*,*trans*-**1a**: **IR** (KBr): 3355, 2931, 2860, 1775, 1740, 1715, 1121; **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 0.90 (t, *J* = 6.8, 3H), 1.26-1.53 (m, 6H), 1.31 (d, *J* = 7.6, 3H), 1.66-1.71 (m, 2H), 3.00 (dq, *J* = 9.2, 7.6, 1H), 3.14 (dd, *J* =

9.2, 6.4, 1H), 4.70 (q, *J* = 6.4, 1H), 9.30 (br s, 1H); **^{13}C NMR** ($CDCl_3$, 100.6 MHz): δ 11.8, 13.9, 22.5, 24.9, 31.3, 34.6, 37.0, 49.9, 79.6, 175.2, 177.5; **HRMS** (EI) calcd for $C_{11}H_{18}O_4$ $[M]^+$ 214.1205, found 214.1214.

Acid (*trans*,*cis*-1a): A similar procedure as for *trans*,*trans*-**1a** was carried out.[14] Thus, pure lactone (*trans*,*cis*-**14a**) (165 mg) afforded *trans*,*cis*-**1a** (124 mg) as a colorless solid in a 93% overall yield: **mp** 136–137 ºC (AcOEt); **$[\alpha]_D$** –114.4º (*c* 1.46, $CHCl_3$) for (2*S*,3S,4*S*)-**1a**; **IR** (KBr) 2958, 1760, 1739, 1260, 1418, 1183; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 0.89 (t, *J* = 6.9, 3H), 1.32 (d, *J* = 7.1, 3H), 1.26-1.44 (m, 5H), 1.55-1.60 (m, 3H), 3.04 (dq, *J* = 10.0, 7.1, 1H), 3.22 (dd, *J* = 10.0, 8.2, 1H), 4.69 (m, 1H); **^{13}C NMR** ($CDCl_3$, 100.6 MHz) δ 13.9, 14.4, 22.4, 25.2, 31.0, 31.3, 36.4, 51.6, 77.3, 174.9, 177.4; **HRMS** (EI) calcd for $C_{11}H_{18}O_4$ $[M]^+$ 214.1205, found 214.1209.

Acid (*cis*,*cis*-1a): A similar procedure as for *trans*,*trans*-**1a** was carried out.[14] Thus, pure lactone (*cis*,*cis*-**14a**) (80 mg) afforded *cis*,*cis*-**1a** (62 mg) as a colorless solid in a 98% overall yield: **mp** 109–110 ºC (AcOEt); **$[\alpha]_D$** –60.6º (*c* 1.81, $CHCl_3$) for (2*S*,3S,4*R*)-**1a**; **IR** (KBr) 2925, 1767, 1700, 1214, 1136; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 0.89 (t, *J* = 6.9, 3H), 1.31 (d, *J* = 6.8, 3H), 1.16-1.88 (m, 8H), 2.95 (dq, *J* = 7.2, 7.2, 1H), 3.33 (dd, *J* = 7.2, 5.2, 1H), 4.44 (m, 1H), 9.52 (br s, 1H); **^{13}C NMR** ($CDCl_3$, 100.6 MHz) δ 10.2, 13.9, 22.3, 25.5, 30.7, 31.3, 39.1, 50.3, 78.9, 175.2, 177.1; **HRMS** (EI) calcd for $C_{11}H_{18}O_4$ $[M]^+$ 214.1205, found 214.1199; Anal. Calcd for $C_{11}H_{18}O_4$: C, 61.66; H, 8.47. Found C, 61.50; H 8.22.

Esterification of acid (1a):

General procedure: Methyl iodide was added to a solution of acid **1a** and $KHCO_3$ in DMF. The mixture was stirred at rt overnight. Then, it was diluted with water (2 mL) and extracted with Et_2O (3 x 5 mL). The organic layer was washed with water (2 x 2 mL), saturated aqueous $NaHSO_3$ and brine. The combined organic layer was dried over $MgSO_4$ and the solvent was removed under vacuum to afford ester **19** that was not further purified.

Ester (*trans*,*trans*-**19a**): Methyl iodide (5 μL, 0.067 mmol), *trans*,*trans*-**1a** (9 mg, 0.042 mmol), $KHCO_3$ (8 mg, 0.84 mmol) and DMF (150 μL) afforded 9 mg (94%) of *trans*,*trans*-**19a** as a colorless oil: **R_f** = 0.15 (9:1 hexane/AcOEt); **IR** (film): 2925, 2854, 1784, 1741, 1173; **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 0.89 (t, *J* = 6.8, 3H), 1.33 (d, *J* = 7.2, 3H), 1.25-1.52 (m, 6H), 1.65-1.79 (m, 2H), 2.65 (dd, *J* = 11.2, 9.6, 1H), 2.96 (dq, *J* = 11.2, 7.2, 1H), 3.78 (s, 3H), 4.45 (ddd, *J* = 9.6, 8.4, 4.4, 1H); **^{13}C NMR** ($CDCl_3$, 100.6 MHz): δ 13.9, 14.5, 22.4, 24.9, 31.4, 34.8, 39.9, 52.6, 54.2, 79.6, 171.2, 176.8; **HRMS** (EI) calcd for $C_{12}H_{20}O_4$ $[M]^+$ 228.1362, found 228.1362.

Ester (*cis*,*trans*-**19a**): Methyl iodide (14 μL, 0.22 mmol), a mixture (1:1) of *cis*,*trans*-**1a** and *trans*,*trans*-**1a** (30 mg, 0.14 mmol), $KHCO_3$ (28 mg, 0.28 mmol) and DMF (450 μL) afforded 32 mg (100%) of a separable mixture (0.9:1) of *cis*,*trans*-**19a** and *trans*,*trans*-**19a** as a colorless oil. Data for *cis*,*trans*-**19a**: **R_f**

= 0.12 (9:1 hexane/AcOEt); **IR** (film): 2925, 2853, 1781, 1740, 1175; **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 0.89 (t, *J* = 6.8, 3H), 1.22 (d, *J* = 7.2, 3H), 1.26-1.54 (m, 6H), 1.64-1.68 (m, 2H), 2.97 (dq, *J* = 9.2, 7.2, 1H), 3.11 (dd, *J* = 9.2, 6.4, 1H), 3.75 (s, 3H), 4.70 (q, *J* = 6.4, 1H); **^{13}C NMR** ($CDCl_3$, 100.6 MHz): δ 11.9, 13.9, 22.4, 25.0, 31.3, 34.7, 37.1, 50.0, 52.1, 79.5, 170.6, 177.3.

*Ester (trans,cis-***19a**): Methyl iodide (33 μL, 0.52 mmol), *trans,cis-***1a** (66 mg, 0.31 mmol), $KHCO_3$ (64 mg, 0.62 mmol) and DMF (600 μL) afforded 67 mg (96%) of *trans,cis-***19a** as a colorless oil: $\mathbf{R_f}$ = 0.68 (98:2 CH_2Cl_2/MeOH); $[\alpha]_D$ –105.1° (*c* 0.735, $CHCl_3$) for (2*S*,3*S*,4*S*)-**19a**; **IR** (film): 2956, 2861, 1781, 1740, 1204, 1075; **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 0.88 (t, *J* = 6.8, 3H), 1.29 (d, *J* = 7.2, 3H), 1.26-1.56 (m, 8H), 3.05 (dq, *J* = 10.0, 7.2, 1H), 3.18 (dd, *J* = 10.0, 8.0, 1H), 3.76 (s, 3H), 4.65 (ddd, *J* = 10.0, 8.4, 3.6, 1H); **^{13}C NMR** ($CDCl_3$, 100.6 MHz): δ 13.9, 14.4, 22.4, 25.2, 31.2, 31.3, 36.3, 51.7, 52.3, 77.5, 170.1, 177.5; **HRMS** (EI) calcd for $C_{12}H_{20}O_4$ $[M]^+$ 228.1362, found 228.1362; Anal. Calcd for $C_{12}H_{20}O_4$: C 63.14, H 8.83. Found C 63.46, H 9.30.

*Ester (cis,cis-***19a**): Methyl iodide (17 μL, 0.27 mmol), *cis,cis-***1a** (36 mg, 0.17 mmol), $KHCO_3$ (34 mg, 0.34 mmol) and DMF (500 μL) afforded 31 mg (80%) of *cis,cis-***19a** as a colorless solid: **mp** 42-43 °C (Et_2O); $\mathbf{R_f}$ = 0.65 (98:2 CH_2Cl_2/MeOH); $[\alpha]_D$ –71.3° (*c* 0.62, $CHCl_3$) for (2*S*,3*S*,4*R*)-**19a**; **IR** (film): 2956, 2861, 1783, 1737, 1175; **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 0.89 (t, *J* = 6.6, 3H), 1.24 (d, *J* = 7.2, 3H), 1.30-1.42 (m, 5H), 1.51-1.61 (m, 2H), 1.75 (m, 1H), 2.90 (quintuplet, *J* = 7.2, 1H), 3.31 (dd, *J* = 7.2, 5.2, 1H), 3.74 (s, 3H), 4.41 (dt, *J* = 8.4, 5.2, 1H); **^{13}C NMR** ($CDCl_3$, 100.6 MHz): δ 10.3, 13.9, 22.4, 25.5, 30.8, 31.4, 39.1, 50.7, 51.7, 79.0, 170.0, 177.0; **HRMS** (EI) calcd for $C_{12}H_{20}O_4$ $[M]^+$ 228.1362, found 228.1364; Anal. Calcd for $C_{12}H_{20}O_4$: C 63.14, H 8.83. Found C 63.43, H 9.04.

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