Tetrahedron: *Asymmetry* 20 (2009) 2121–2124

Contents lists available at ScienceDirect

Tetrahedron: *Asymmetry*

journal homepage: www.elsevier.com/locate/tetasy

A concise synthesis of highly enantiomerically enriched 2-alkylparaconic acid esters via ruthenium-catalyzed asymmetric hydrogenation of acylsuccinates

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ARTICLE INFO

Article history:
Received 30 June 2009
Accepted 4 September 2009
Available online 30 September 2009

ABSTRACT

The catalytic asymmetric hydrogenation of acylsuccinates using $RuCl_3$ as a precatalyst and atropisomeric diphosphines as chiral auxiliaries allows the synthesis of optically active 2-alkylparaconic acid esters in preparative yields with enantioselectivities up to 99.5% ee.

1. Introduction

Chiral 5-oxo-tetrahydrofuran-3-carboxylic acid,[1] known as paraconic acid **1**, is an important structural unit for certain natural compounds and their analogues. Although acid **1** is not found by itself in nature, its derivatives bearing a long-chain alkyl group (C_5–C_{13}) at the 2-position and the methyl or methylene group at position 4, such as acids **2**–**6** (Fig. 1), can be isolated from different natural sources, including mosses, lichens, and fungi. In the last few years, these types of derivatives have attracted increasing attention due to their valuable properties, such as relevant antitumor, antibiotic, and anti-inflammatory activities.[2]

However, natural sources commonly contain hard-to-separate mixtures of structurally similar derivatives of compound **1**. This has stimulated the development of different approaches to the synthesis of acids **2**–**6** and their analogues using chiral auxiliaries,[3] enzymatic methods,[4] and asymmetric catalysis by transition metal complexes.[5]

Some chiral derivatives of acid **1** have been shown to be useful building blocks.[6] Among them, chiral 2-alkylparaconic acids **7** (Fig. 2) and their derivatives are of particular interest as model substrates[6a,b] for the preparation of compounds, which may have a different pharmacological activity pattern.

Acids of type **7** containing two stereogenic carbon atoms are difficult to prepare according to known methods, which usually include several steps with the involvement of organometallic or difficult-to-use reagents.[3a–c,i–k,n] The asymmetric reduction of acylsuccinates offers a promising route to chiral 2-alkylparaconic acids. Thus, a high enantioselectivity was achieved using the baker's yeast reduction of diethyl acetylsuccinate to form diethyl 2-(1-hydroxyethyl)succinate, whose cyclization gave a mixture of ethyl (2*S*,3*S*)- and ethyl (2*S*,3*R*)-2-methylparaconates of enantiomeric purity >99% ee.[6a] However, in the case of the bioreduction of other diesters of acylsuccinic acids **7**, chemical yields and enantiomeric excesses of chiral products turned out to be greatly dependent on the bulkiness of acyl and ester groups in the starting reagents.[6a]

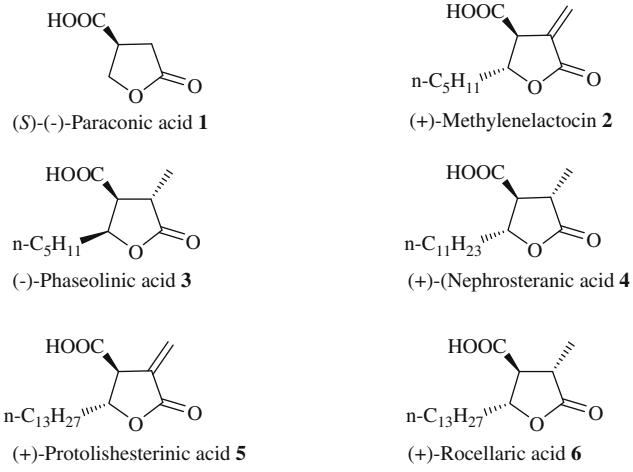

Figure 1. Paraconic acid and its naturally occurred derivatives.

Herein, we report the ruthenium-catalyzed asymmetric hydrogenation of acylsuccinates and the synthesis of chiral 2-alkylsubstituted paraconic acid esters.

2. Results and discussion

Previously, we have reported[5b,c] the enantioselective synthesis of chiral γ-alkylated butyrolactones via asymmetric hydrogenation

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doi:10.1016/j.tetasy.2009.09.006

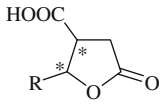


Figure 2. Chiral 2-alkylparaconic acids (R = C_1–C_5) (**7**).

of γ-ketoesters in the presence of the readily available catalytic systems (COD)Ru(2-methylallyl)$_2$–BINAP–HCl or $RuCl_3$–BINAP–HCl. Catalytic systems containing the precatalyst $RuCl_3$ and chiral diphosphines are currently used to prepare chiral 2-alkylparaconic acid esters from acylsuccinates **8** (Scheme 1). To the best of our knowledge, the reported reaction is the first example of an asymmetric hydrogenation of acylsuccinates catalyzed by chiral transition metal complexes.

The hydrogenation of acylsuccinate **8** affords chiral hydroxy diester **9**, which undergoes cyclization under the reaction conditions to give a mixture of *trans*- and *cis*-isomers of 2-alkylparaconic acid esters **10** and **11**. As opposed to the ruthenium-catalyzed hydrogenation of simple γ-ketoesters,[5b,c,7] HCl has little influence on the catalyst activity in the hydrogenation of acylsuccinates **8**, which can be considered not only as a γ-ketoester but also as a more reactive β-ketoester.

2.1. Asymmetric hydrogenation of dimethyl acetylsuccinate

To compare the efficiency of different catalytic systems in the hydrogenation of acylsuccinates and to investigate the stereochemistry of this reaction, we chose dimethyl acetylsuccinate **8a** as a model substrate.

2.1.1. Influence of the nature of chiral ligands

Different catalytic systems containing $RuCl_3$ and chiral diphosphine were examined with the aim of performing the asymmetric hydrogenation of acylsuccinate **8a**; however, only atropisomeric ligands are highly efficient (Table 1). Other types of bisphosphines, such as ProPHOS, Me- and Pr^i-DuPHOS, proved to be virtually inert in this reaction under the same conditions. The application of catalytic systems containing chiral diphosphines BINAP or SynPHOS or their analogues in the asymmetric hydrogenation of acetylsuccinate **8a** allows us to obtain the *trans*- and *cis*-isomers **10a** and **11a** with a conversion up to 100% and with an enantioselectivity of 87–95 and 94.5–98% ee respectively. Similar ee values were obtained in the hydrogenation of other acylsuccinates (Table 2). It is remarkable that an appreciably higher enantioselectivity of the formation of *cis*-lactone esters compared to the corresponding *trans*-isomers has been recently observed for the enzymatic hydrolysis of 2-arylparaconates.[6d]

2.1.2. Study of the stereochemistry of hydrogenation

The absolute configuration of the C-2 stereocenter of lactones **10a** and **11a** was (2*R*) assigned based on the sign of specific rotation of the known[6a] enantiomers (−)-(2*S*,3*R*)-**10a** and (−)-(2*S*,3*S*)-**11a**. The *trans*- and *cis*-geometries for the lactones were assigned by comparing their ^{1}H and ^{13}C NMR spectra with those of their

Table 1
Asymmetric hydrogenation of acylsuccinate **8a** using different chiral ligands[a]

Entry	Ligand (*R*)	Conversion (%)	Products (%)		ee (%)	
			10a	**11a**	**10a** (2*R*,3*S*)	**11a** (2*R*,3*R*)
1	BINAP	100	64	36	87	97
2	Tol-BINAP	73	68	32	94.5	98.5
3	3,5-Xylyl-BINAP	87	69	31	89.5	94.5
4	SynPHOS	100	65	35	95	98

[a] [$RuCl_3$]/[Ligand] = 1/1.05, [**8a**]/[Ru] = 200, [S] = 3.9–4.1 M, solvent—abs MeOH, 40 atm H_2, 60 °C, 2 h.

Table 2
Hydrogenation of acylsuccinates in the presence of the $RuCl_3$–(*R*)-BINAP catalytic system[a]

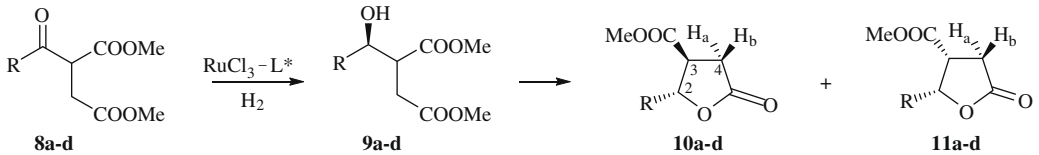
Acyl-succinate	[**8**]/[Ru]	*t* (h)	Products		ee (%)	
			Yield[b] (%)	**10**/**11**	**10**	**11**
8a	500	2	72	65/35	89.5	98
8b	250	2	69	60/40	94	99
8b	500	6	70	60/40	92	98
8c	250	6	75	55/45	96	98.5
8d	250	15	40	95/5	84	99.5

[a] $RuCl_3$/(*R*)-BINAP = 1/1.05; solvent—abs MeOH; [**8**] = 2.2–2.4 M, 40 atm H_2, 60 °C.
[b] For the isolated mixture of **10** and **11**.

enantiomers,[6a] as well as based on the results of NOESY experiments. Thus, the NOESY correlations for *trans*-isomer **10a** showed intense cross-peaks corresponding to through-space interactions between CH_3 and H-3, as well as between CH_3 and H-4(A). At the same time, virtually no cross-peaks are observed between the *trans*-CH_3 and H-4(B) of **10a**. This is evidence that all the above atoms, except for H-4(B), are on the same side of the plane of the ring in **10a**. On the contrary, the NOESY spectrum of *cis*-isomer **11a** shows an intense cross-peak assigned to the interaction between H-2 and H-3, but there are no obvious cross-peaks for CH_3 and H-3.

2.2. Synthesis of chiral 2-alkylparaconic acid esters

The stereochemistry of the hydrogenation of acylsuccinates other than **8a** was also established by NMR spectroscopy. On the whole, the stereochemistry is the same, except for the difference in the ratio of *trans*- to *cis*-isomeric lactones generated from substrates **8a**–**d**. As can be seen from Table 2, the hydrogenation of acylsuccinates **8a**–**c** in the presence of the catalytic system $RuCl_3$–(*R*)-BINAP gave lactones **10a**–**c** and **11a**–**c** in ratios of 55–65/45–35, whereas the hydrogenation of acylsuccinate **8d** proceeded with a much higher diastereoselectivity (**10d**/**11d** = 95/5) probably due to the steric effect of the isopropyl group. It is noteworthy that the enantiomeric purity of *cis*-lactones **11c**–**d**, such as that of **11a** (Table 1), proved to be markedly higher (97–99.5% ee) than that of the *trans*-isomers (84–96% ee) in the case of using the



8a-d **9a-d** **10a-d** **11a-d**

R = Me (**a**), Et (**b**), Pr (**c**), Pr^i (**d**); L* = atropisomeric diphosphine ligand

Scheme 1. Synthesis of chiral methyl 2-alkylparaconates.

same chiral ligand. Individual chiral *cis*- and *trans*-diastereomeric lactones were isolated by column chromatography and their physicochemical and spectroscopic characteristics were determined.

3. Conclusions

In conclusion, the asymmetric hydrogenation of acylsuccinates in the presence of the readily available catalytic system $RuCl_3$–atropisomeric diphosphine allows the synthesis of chiral 2-alkylparaconic acid esters in preparative yields and with enantioselectivities up to 99.5% ee.

4. Experimental

4.1. General

The starting acylsuccinates **8a–d** were prepared by the free-radical addition of aliphatic aldehydes to dimethyl maleate.[5b] Commercial anhydrous $RuCl_3$ and (*R*)-BINAP (Aldrich), Tol-BINAP, 3,5-Xylyl-BINAP, and SynPHOS (Strem) were used without additional purification. Prior to use, all the solvents were dehydrated and distilled in a stream of argon. Argon was purified by passing through columns containing a nickel–chromium catalyst, copper supported on Kieselguhr (80 °C), and molecular sieves (4 Å). Hydrogen was purified by passing through columns with a nickel–chromium catalyst and molecular sieves. Column chromatography was performed using a 14.5 × 380 mm column packed with Silica Gel 60 (Fluka) with the use of petroleum ether/diethyl ether (20%) as the eluent. An enantiomeric analysis of lactones was carried out by GLC on a Biochrom-21 chromatograph equipped with a quartz capillary column (30 m × 0.2 mm × 0.25 μm) using 2,6-dipentyl-3-(fluoroacetyl)-β-cyclodextrin as the stationary phase. Optical rotations were determined on a PU-09 spectropolarimeter (State Research Center for Scientific Instrument Making at the Bauman Moscow State Technical University). ^{1}H and ^{13}C NMR spectra were registered by Bruker AM-300. IR spectra were recorded on a Specord M80-1 instrument. Mass spectroscopy was performed on a Kratos MS-30 device (70 eV).

4.2. General procedure for asymmetric hydrogenation

(*R*)-BINAP (10.3 mg, 0.0165 mmol) and anhydrous $RuCl_3$ (3.3 mg, 0.0159 mmol) were placed into a pre-evacuated and argon-filled glass tube. Acylsuccinate **8** (8.0 mmol) was dissolved in abs MeOH (4 mL), and the solution was degassed using three freezing–evacuation–thawing–argon-filling cycles. The degassed solution was poured into the tube for hydrogenation, and the tube was placed in a stainless-steel autoclave (50 mL) pre-filled with argon. Then the autoclave was purged with purified hydrogen and pressurized with H_2 up to 40 atm. The reaction mixture was magnetically stirred (700 rpm) for the selected time. The solvent was evaporated. The distillation of the residue under reduced pressure gave a mixture of lactones **10** and **11**. A part (300 mg) of the mixture was separated by column chromatography using petroleum ether/diethyl ether (80/20) as the eluent.

4.3. Methyl 2-alkyl-5-oxo-tetrahydrofuran-3-carboxylates 10 and 11

4.3.1. Methyl (2R,3S)-2-methyl-5-oxo-tetrahydrofuran-3-carboxylate 10a

Yield: 105 mg, oil; R_f = 0.35. IR, cm^{-1}: 1788, 1736. GLC [retention time (t_R), min, He, 145 °C]: CH_4 (non-sorbable component), 1.1; (2*S*,3*R*), (minor), 3.6; (2*R*,3*S*), (major), 3.8; $[\alpha]_D^{20} = +33.0$ (*c* 0.216, CH_2Cl_2), $[\alpha]_D^{20} = +32.9$ (*c* 0.23, CH_3CN) [lit.[3] (2*S*,3*R*) −34.4 (*c* 0.16, CH_3CN)]. ^{1}H NMR (δ, ppm, $CDCl_3$): 4.69–4.58 (m, 1H, MeC*H*), 3.72 (s, 3H, OMe), 3.03–2.69 (m, 3H, $CHCH_2CO$), 1.46 (d, *J* = 6.3 Hz, 3H, *Me*CH). ^{13}C NMR (δ, ppm, $CDCl_3$): 174.28 (CH_2CO) 171.19 (*C*OOMe), 78.14 (MeCHO), 52.63 (COO*Me*), 47.33 (*C*HCOOMe), 32.25 (CH_2CO), 20.70 (*Me*CHO). MS, *m/z*: 158 (7), 130 (20), 127 (37), 114 (69), 101 (34), 99 (65), 83 (79), 71 (27), 69 (33), 59 (100), 55 (88), 43 (20). Anal. Calcd for $C_7H_{10}O_4$: C, 53.16; H, 6.37. Found: C, 52.89; H, 6.15.

4.3.2. Methyl (2*R*,3*R*)-2-methyl-5-oxo-tetrahydrofuran-3-carboxylate 11a

Yield: 83.5 mg, oil; R_f = 0.27. IR, cm^{-1}: 1788, 1736. GLC [retention time (t_R), min, He, 145 °C]: CH_4 (non-sorbable component), 1.1; (2*R*,3*R*), (major), 4.8; (2*S*,3*S*), (minor), 5.1; $[\alpha]_D^{20} = +79.9$ (*c* 0.158, CH_2Cl_2), $[\alpha]_D^{20} = +83.2$ (*c* 0.194, CH_3CN) [lit.[3] (2*S*,3*S*) −77.1 (*c* 0.14, CH_3CN)]. ^{1}H NMR (δ, ppm, $CDCl_3$): 4.88–4.78 (m, 1H, MeC*H*), 3.72 (s, 3H, OMe), 3.49–3.40 (m, 1H, *C*HCH_2CO), 2.91 (dd, *J* = 17.7 Hz, *J* = 6.3 Hz, 1H, CH_aH_bCO), 2.65 (dd, *J* = 17.7 Hz, *J* = 8.8 Hz, 1H, CH_aH_bCO), 1.30 (d, *J* = 6.5 Hz, 3H, MeCH). ^{13}C NMR (δ, ppm, $CDCl_3$): 174.81 (CH_2CO) 170.69 (*C*OOMe), 76.32 (MeCHO), 52.27 (COO*Me*), 44.53 (*C*HCOOMe), 31.28 (CH_2CO), 16.84 (*Me*CHO). MS, *m/z*: 158 (17), 143 (45), 128 (24), 127 (64), 126 (40), 114 (90), 113 (36), 101 (16), 100 (27), 99 (74), 83 (77), 72 (34), 71 (41), 69 (19), 59 (74), 55 (100), 43 (11). Anal. Calcd for $C_7H_{10}O_4$: C, 53.16; H, 6.37. Found: C, 52.92; H, 6.19.

4.3.3. Methyl (2*R*,3*S*)-2-ethyl-5-oxo-tetrahydrofuran-3-carboxylate 10b

Yield: 115.3 mg, oil; R_f = 0.37. IR, cm^{-1}: 1784, 1740. GLC [retention time (t_R), min, He, 145 °C]: CH_4 (non-sorbable component), 1.1; (2*S*,3*R*), (minor), 4.7; (2*R*,3*S*), (major), 5.0; $[\alpha]_D^{20} = +39.8$ (*c* 0.17, CH_2Cl_2), $[\alpha]_D^{20} = +38.2$ (*c* 0.202, CH_3CN). ^{1}H NMR (δ, ppm, $CDCl_3$): 4.55–4.46 (m, 1H, EtC*H*), 3.73 (s, 3H, OMe), 3.10–2.99 (m, 1H, *C*HCH_2CO), 2.89 (dd, *J* = 17.7 Hz, *J* = 8.6 Hz, 1H, CH_aH_bCO), 2.75 (dd, *J* = 17.7 Hz, *J* = 9.6 Hz, 1H, CH_aH_bCO), 1.89-1.65 (m, 2H, MeCH_2CH), 1.05 (t, *J* = 7.4 Hz, 3H, *Me*CH_2CH). ^{13}C NMR (δ, ppm, $CDCl_3$): 174.28 (CH_2CO) 171.19 (*C*OOMe), 82.87 (EtCHO), 52.48 (COO*Me*), 44.91 (*C*HCOOMe), 32.00 (CH_2CO), 28.05 (MeCH_2CH), 9.18 (*Me*CH_2CH). MS, *m/z*: 172 (10), 155 (20), 144 (83), 143 (93), 131 (42), 130 (79), 115 (100), 101 (44), 99 (31), 83 (68), 74 (38), 71 (46), 69 (96), 59 (61), 55 (68), 43 (4). Anal. Calcd for $C_8H_{12}O_4$: C, 55.81; H, 7.02. Found: C, 55.63; H, 6.86.

4.3.4. Methyl (2*R*,3*R*)-2-ethyl-5-oxo-tetrahydrofuran-3-carboxylate 11b

Yield: 93.8 mg, oil; R_f = 0.29. IR, cm^{-1}: 1784, 1740. GLC [retention time (t_R), min, He, 145 °C]: CH_4 (non-sorbable component), 1.1; (2*R*,3*R*), (major), 6.3; (2*S*,3*S*), (minor), 6.8; $[\alpha]_D^{20} = +105.4$ (*c* 0.234, CH_2Cl_2), $[\alpha]_D^{20} = +104.4$ (*c* 0.198, CH_3CN). ^{1}H NMR (δ, ppm, $CDCl_3$): 4.59–4.49 (m, 1H, EtC*H*), 3.72 (s, 3H, OMe), 3.49–3.39 (m, 1H, *C*HCH_2CO), 2.75 (dd, *J* = 17.6 Hz, *J* = 5.5 Hz, 1H, CH_aH_bCO), 2.64 (dd, *J* = 17.6 Hz, *J* = 8.7 Hz, 1H, CH_aH_bCO), 1.63-1.50 (m, 2H, MeCH_2CH), 1.01 (t, *J* = 7.4 Hz, 3H, *Me*CH_2CH). ^{13}C NMR (δ, ppm, $CDCl_3$): 174.81 (CH_2CO) 170.77 (*C*OOMe), 81.69 (EtCHO), 52.03 (COO*Me*), 43.94 (*C*HCOOMe), 31.74 (CH_2CO), 24.54 (MeCH_2CH), 10.07 (*Me*CH_2CH). MS, *m/z*: 172 (14), 155 (20), 154 (47), 144 (50), 143 (100), 140 (60), 130 (10), 128 (15), 126 (33), 115 (88), 99 (17), 95 (16), 83 (50), 74 (20), 71(20), 69 (59), 59 (45), 55 (79), 43 (7). Anal. Calcd for $C_8H_{12}O_4$: C, 55.81; H, 7.02. Found: C, 55.68; H, 6.91.

4.3.5. Methyl (2*R*,3*S*)-2-propyl-5-oxo-tetrahydrofuran-3-carboxylate 10c

Yield: 115.5 mg, oil; R_f = 0.48. IR, cm^{-1}: 1784, 1740. GLC [retention time (t_R), min, He, 145 °C]: CH_4 (non-sorbable component), 1.1; (2*S*,3*R*), (minor), 5.9; (2*R*,3*S*), (major), 6.4; $[\alpha]_D^{20} = +39.3$ (*c*

0.186, CH_2Cl_2), $[\alpha]_D^{20} = +39.4$ (*c* 0.164, CH_3CN). ^1H NMR (δ, ppm, $CDCl_3$): 4.52–4.44 (m, 1H, PrC*H*), 3.67 (s, 3H, OMe), 3.03–2.93 (m, 1H, C*H*CH_2CO), 2.80 (dd, *J* = 17.8 Hz, *J* = 8.5 Hz, 1H, C$H_a$$H_b$CO), 2.67 (dd, *J* = 17.8 Hz, *J* = 9.7 Hz, 1H, CH_aH_bCO), 1.69-1.59 (m, 2H, MeCH_2*C*H_2CH), 1.50-1.26 (m, 2H, Me*C*$H_2$$CH_2$CH), 0.87 (t, *J* = 7.4 Hz, 3H, *Me*$CH_2$$CH_2$CH). ^{13}C NMR (δ, ppm, $CDCl_3$): 174.26 (CH_2*C*O) 171.45 (*C*OOMe), 81.47 (PrCHO), 52.39 (COO*Me*), 45.31 (*C*HCOOMe), 37.10 (MeCH_2*C*H_2CH), 31.85 (*C*H_2CO), 18.31 (Me$CH_2$$CH_2$CH), 13.42 (*Me*$CH_2$$CH_2$CH). MS, *m/z*: 186 (9), 158 (50), 155 (53), 144 (88), 143 (97), 130 (25), 127 (28), 126 (45), 115 (100), 101 (35), 99 (28), 83 (67), 74 (27), 71 (85), 69 (54), 59 (50), 55 (86), 43 (11). Anal. Calcd for $C_9H_{14}O_4$: C, 58.05; H, 7.58. Found: C, 57.84; H, 7.45.

4.3.6. Methyl (2*R*,3*R*)-2-propyl-5-oxo-tetrahydrofuran-3-carboxylate 11c

Yield: 90.9 mg, solid, mp 42 °C, R_f = 0.38. IR, cm^{-1}: 1784, 1740. GLC [retention time (t_R), min, He, 145 °C]: CH_4 (non-sorbable component), 1.1; (2*R*,3*R*), (major), 7.7; (2*S*,3*S*), (minor), 8.4; $[\alpha]_D^{20} = +94.0$ (*c* 0.328, CH_2Cl_2), $[\alpha]_D^{20} = +93.2$ (*c* 0.16, CH_3CN). ^1H NMR (δ, ppm, $CDCl_3$): 4.58–4.49 (m, 1H, PrC*H*), 3.63 (s, 3H, OMe), 3.40–3.30 (td, *J* = 15.6 Hz, *J* = 5.1 Hz, 1H, C*H*CH_2CO), 2.73 (dd, *J* = 17.5 Hz, *J* = 5.0 Hz, 1H, C$H_a$$H_b$CO), 2.58 (dd, *J* = 17.5 Hz, *J* = 8.6 Hz, 1H, CH_aH_bCO), 1.65-1.23 (m, 4H, MeCH_2*C*H_2CH), 0.84 (t, *J* = 7.0 Hz, 3H, *Me*$CH_2$$CH_2$CH). ^{13}C NMR (δ, ppm, $CDCl_3$): 174.86 (CH_2*C*O) 170.89 (*C*OOMe), 80.04 (PrCHO), 51.93 (COO*Me*), 44.00 (*C*HCOOMe), 33.14 (MeCH_2*C*H_2CH), 31.74 (*C*H_2CO), 18.91 (Me$CH_2$$CH_2$CH), 13.42 (*Me*$CH_2$$CH_2$CH). MS, *m/z*: 186 (8), 168 (15), 155 (61), 154 (49), 144 (41), 143 (89), 140 (45), 130 (9), 127 (32), 126 (71), 115 (88), 101 (17), 99 (16), 83 (77), 74 (15), 72 (22), 71 (65), 69 (29), 59 (49), 55 (100), 43 (12). Anal. Calcd for $C_9H_{14}O_4$: C, 58.05; H, 7.58. Found: C, 57.79; H, 7.40.

4.3.7. Methyl (2*R*,3*S*)-2-isopropyl-5-oxo-tetrahydrofuran-3-carboxylate 10d

Yield: 100.5 mg, R_f = 0.50. IR, cm^{-1}: 1784, 1740. GLC [retention time (t_R), min, He, 145 °C]: CH_4 (non-sorbable component oil,), 1.1; (2*S*,3*R*), (minor), 5.4; (2*R*,3*S*), (major), 5.8; $[\alpha]_D^{20} = +23.9$ (*c* 0.304, CH_2Cl_2), $[\alpha]_D^{20} = +24.9$ (*c* 0.318, CH_3CN). ^1H NMR (δ, ppm, $CDCl_3$): 4.39–4.33 (m, 1H, *i*-PrC*H*), 3.69 (s, 3H, OMe), 3.12–3.03 (m, 1H, C*H*CH_2CO), 2.82 (dd, *J* = 17.9 Hz, *J* = 7.9 Hz, 1H, C$H_a$$H_b$CO), 2.70 (dd, *J* = 17.9 Hz, *J* = 9.9 Hz, 1H, CH_aH_bCO), 1.94-1.80 (m, 1H, Me_2*C*HCH), 0.93 (t, *J* = 6.4 Hz, 6H, *Me*$_2$CHCH). ^{13}C NMR (δ, ppm, $CDCl_3$): 174.31 (CH_2*C*O) 172.13 (*C*OOMe), 86.33 (*i*-PrCHO), 52.47 (COO*Me*), 42.61 (*C*HCOOMe), 32.34 (*C*H_2CO), 32.32 (MeCH(Me)CH), 17.55 (*Me*CH(Me)CH), 17.02 (MeCH(*Me*)CH). MS, *m/z*: 186 (6), 158 (42), 155 (50), 144 (83), 143 (100), 127 (31), 126 (60), 115 (97), 101 (38), 99 (16), 83 (84), 74 (21), 72 (27), 71 (70), 69 (38), 59 (54), 55(70), 43 (10). Anal. Calcd for $C_9H_{14}O_4$: C, 58.05; H, 7.58. Found: C, 57.79; H, 7.39.

4.3.8. Methyl (2*R*,3*R*)-2-isopropyl-5-oxo-tetrahydrofuran-3-carboxylate 11d

Yield: 7 mg, solid, mp 92 °C, R_f = 0.66. IR, cm^{-1}: 1784, 1740. GLC [retention time (t_R), min, He, 145 °C]: CH_4 (non-sorbable component), 1.1; (2*R*,3*R*), (major), 7.7; (2*S*,3*S*), (minor), 8.0; $[\alpha]_D^{20} = +38.0$ (*c* 0.108, CH_2Cl_2). ^1H NMR (δ, ppm, $CDCl_3$): 4.2 (dd, *J* = 8.8 Hz, *J* = 6.3 Hz, 1H, *i*-PrC*H*), 3.76 (s, 3H, OMe), 3.47–3.37 (m, 1H, C*H*CH_2CO), 2.82 (dd, *J* = 17.4 Hz, *J* = 3.6 Hz, 1H, C$H_a$$H_b$CO), 2.70 (dd, *J* = 17.4 Hz, *J* = 7.9 Hz, 1H, CH_aH_bCO), 1.94-1.75 (m, 1H, Me_2*C*HCH), 1.09 (d, *J* = 6.5 Hz, 3H, *Me*(Me)CHCH), 1.00 (d, *J* = 6.5 Hz, 3H, Me(*Me*)CHCH). ^{13}C NMR (δ, ppm, $CDCl_3$): 174.36 (CH_2*C*O), 170.75 (*C*OOMe), 85.78 (*i*-PrCHO), 51.74 (COO*Me*), 43.40 (*C*HCOOMe), 32.97 (*C*H_2CO), 29.85 (Me*C*H(Me)CH), 18.91 (*Me*CH(-Me)CH), 17.96 (MeCH(*Me*)CH). MS, *m/z*: 186 (27), 168 (24), 155 (50), 144 (69), 143 (69), 140 (31), 127 (24), 126 (45), 115 (80), 101 (12), 99 (33), 83 (100), 72 (38), 71 (41), 69 (79), 55(63), 43 (7). Anal. Calcd for $C_9H_{14}O_4$: C, 58.05; H, 7.58. Found: C, 57.79; H, 7.39.

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