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Asymmetric synthesis of quaternary α-amino acids using D-ribonolactone acetonide as chiral auxiliary

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Abstract

We describe a new simple methodology to prepare enantiopure α,α-dialkylglycines based on the use of commercially available D-ribonolactone as a chiral auxiliary. Enantiopure α-methyl and α-butyl series are prepared through diastereoselective alkylation and subsequent Schmidt rearrangement of α,α-dialkylacetoacetates of D-ribonolactone acetonide. Absolute configuration was assigned through preparation of enantiopure 4,4-disubstituted 3-methyl-2-pyrazolin-5-ones.

1. Introduction

The high interest in the preparation of enantiomerically pure α,α-disubstituted glycines is based on their remarkable properties as enzyme inhibitors[1] and as conformational modifiers of peptides.[2] In particular the α-methyl series have been extensively studied.[3]

Due to the current interest in these compounds many synthetic methodologies have already been developed.[4] One synthetic approach is the use of cyclic derivatives such as Schöllkopf's bis(lactim)ether, prepared generally from L-*tert*-leucine and including two amino ester separations in the process of isolation of desired products. Others cyclic substrates are Seebach's oxazolidinones, imidazolidinones and 2,5-dihydroimidazoles,[5] their synthesis including classical resolution through diastereoisomeric salt formation or chromatographic separation on a chiral column. Nájera's oxazinones and tetrahydropyrazinones[6] have also been used with real success. Also remarkable are the results of Davies, who has used oxazolidinones derived from ferrocenecarbaldehyde and sodium (*S*)-alaninate,[7] and the work of Sandri using chiral morpholine derivatives.[8] An alternative involves the palladium-catalyzed asymmetric allylation of azlactones.[9]

A different approach is based on the diastereoselective alkylation of activated methylene groups in open chain compounds (Fig. 1). Remarkable diastereoselective alkylations have been achieved for 2-cyanoesters of enantiopure dicyclohexylsulfamoylisoborneol by Cativiela and co-workers[10] (**1**, Z=CN).

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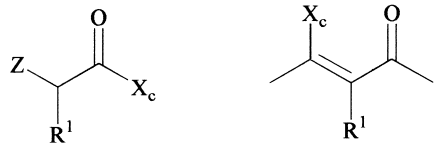
After the appropriate rearrangement process the diastereomerically pure α,α-dialkylcyanoacetate can be elaborated to afford both enantiomers of the same amino acid. An alternative consists of the incorporation of the chiral auxiliary in the form of an enamine **2**. Koga has reported[11] the alkylation of lithioenamines derived from α-alkyl-β-ketoesters and (*S*)-valine *tert*-butyl ester. The α,α-dialkyl-β-ketoesters obtained had been used by Georg et al. as intermediates to prepare α,α-disubstituted glycines.[12] Fukumoto et al. have worked on chiral derivatives of malonic acid. Precursors of amino acids are prepared through diastereoselective alkylation of 8-phenylmenthyl α-alkylmalonic monoesters (**1**, Z=COOH) followed by several transformations including a Curtius rearrangement.[13] Herein we describe the use of D-ribonolactone acetonide as a chiral auxiliary in the rearrangement of β-ketoacid derivatives, an established strategy for the synthesis of quaternary α-amino acids.



1 **2**

Figure 1.

We have previously reported the preparation of enantiopure diphenylmethyl-, 9-fluorenyl- and (1-adamantyl)glycines through cobalt mediated alkylation of (4*R*)- and (4*S*)-3-acetoacetyl-4-benzyloxazolidin-2-ones (**1**, *Z*=acetyl, R^1=H).[14] Several dialkylation attempts on the same substrate failed. However, alkylation of (−)-8-phenylmenthyl 2-methylacetoacetate affords 8-phenylmenthyl 2-alkyl-2-methylacetoacetates in a maximal diastereomeric ratio of 85:15.[15] Subsequent elaboration to amino acids failed, probably due to steric hindrance. These previous results led us to consider other alcohols as chiral auxiliaries. We chose D-ribonolactone[16] for two main reasons: (a) it is a commercially available sugar derivative; and (b) being a primary alcohol, its ester might be easily manipulated (this has failed in the case of (−)-8-phenylmenthol).

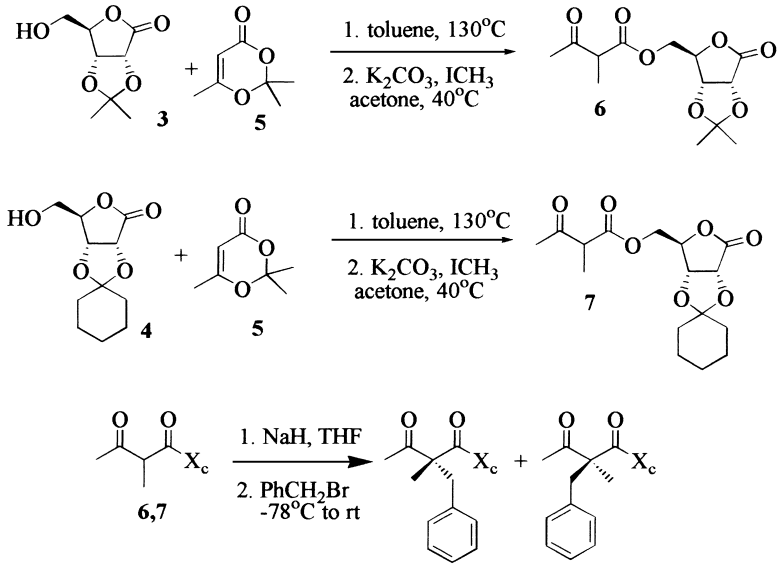
2. Results and discussion

2,3-*O*-Isopropylidene-[17] and 2,3-*O*-cyclohexylidene-γ-D-ribonolactone[18] had been prepared by reactions described previously in the literature. These protected lactones react with 2,2,6-trimethyl-1,3-dioxen-4-one **5** in refluxing toluene (74–82% yield), followed by addition of potassium carbonate and methyl iodide in acetone at 40°C to afford the corresponding 2-methyl acetoacetates **6** and **7** (Scheme 1). We first studied the dialkylation process through generation of enolate with NaH at −78°C and subsequent addition of benzyl bromide, and we obtained a similar d.r. for the two chiral auxiliaries. In the case of cyclohexylidene protection we were unable to isolate the major diastereoisomer in pure form. Therefore, we chose 2,3-*O*-isopropylidene-γ-D-ribonolactone as the chiral auxiliary.

Some attempts have been made to optimize the process: (a) other bases such as LDA, phosphazene P_4-*t*-Bu in *n*-hexane ($C_{22}H_{63}N_{13}P_4$) and sodium bis(trimethylsilyl)amide gave similar or worse d.r.s; and (b) addition of *N*,*N*′-dimethylpropyleneurea (DMPU) or change of THF to DMPU, when using NaH, did not give better results.

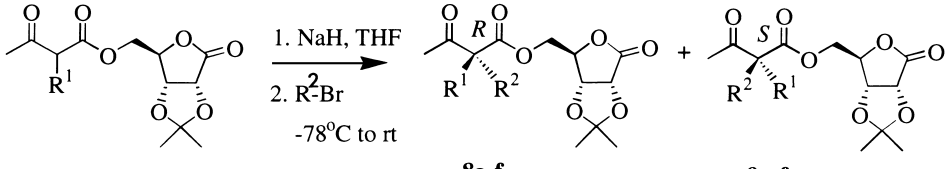
Alkylation of **6** with a series of alkyl halides furnished compounds **8a**–**d** and **9a**–**d** in reasonable diastereomeric excesses (Table 1). The major diastereoisomers were isolated in pure form in all cases except for R^2=PhCH=CHCH$_2$.

We were also interested in disubstituted glycines with one group different from methyl. Compound **12** was easily prepared from 2,3-*O*-isopropylidene-γ-D-ribonolactone acetoacetate with NaH in refluxing



Scheme 1.

Table 1
Results of diastereoselective dialkylation of **6** and **12** with a series of alkyl halides



6 ($R^1 = CH_3$)
12 (R^1 = Bu)

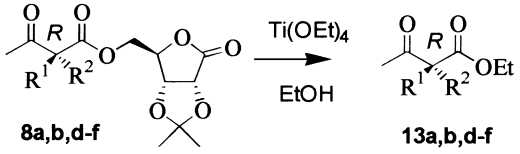
R^1	R^2	products[a]	yield (%)	dr
CH_3	$PhCH_2$	**8a+9a**	69	75:25
CH_3	4-$BrPhCH_2$	**8b+9b**	64	78:22
CH_3	$PhCH{=}CHCH_2$	**8c+9c**	71	80:20
CH_3	2-$NaphtCH_2$	**8d+9d**	74	80:20
Bu	4-$BrPhCH_2$	**8e+9e**	75	80:20
Bu	2-$NaphtCH_2$	**8f+9f**	69	80:20

[a] All pure diastereoisomers **8a,b,d-f** and **9a,b,d-f** and the mixture **8c+9c** gave correct elemental analysis (C, H).

THF and *n*-butyl iodide in 71% yield. Even with the bulkier *n*-butyl substituent high yields are obtained in the dialkylation process (Table 1).

Table 2 summarizes the results for transesterification of pure diastereoisomers **8a**,**b**,**d**–**f**. By using an excess of titanium(IV) tetraethoxide in refluxing ethanol the corresponding enantiopure ethyl α,α-dialkyl acetoacetates are obtained in excellent yields when $R^1{=}CH_3$. Experiments with sodium ethoxide gave worse results. For a butyl substituent as in compounds **8e**,**f**, less efficient reactivity was found, as expected.

Table 2
Results of transesterification reaction

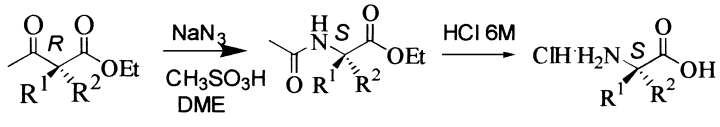


R^1	R^2	products[a]	bp (mmHg)	yield (%)
CH_3	$PhCH_2$	**13a**[11,19]	125 °C (0.07)	92
CH_3	4-$BrPhCH_2$	**13b**	150 °C (0.07)	90
CH_3	2-$NaphtCH_2$	**13d**	175 °C (0.07)	93
Bu	4-$BrPhCH_2$	**13e**	150 °C (0.07)	37
Bu	2-$NaphtCH_2$	**13f**	-	49

[a] All products **13** gave correct elemental analysis (C, H).

Schmidt rearrangement of **13** with sodium azide and methanesulfonic acid in dimethoxyethane afforded acetamides **14** (Table 3). We have previously recommended the use of DME as an alternative to the unsafe chlorinated solvents normally used in Schmidt rearrangement.[20] Acetamides **14** were hydrolyzed in refluxing 6 M HCl to give the amino acid hydrochlorides **15** in excellent yields (Table 3).

Table 3
Schmidt reaction of α,α-disubstituted acetoacetates **13** and posterior hydrolysis of acetamides **14**



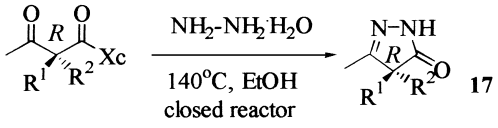
R^1	R^2	**14** (%)[a]	**15** (%)[b]	**15**, $[\alpha]_D$
CH_3	$PhCH_2$	**14a**[13b] (82)	**15a** (81)	-7 (c = 1.22, H_2O)
CH_3	4-$BrPhCH_2$	**14b** (63)	**15b** (81)	-8 (c = 1.05, H_2O)
CH_3	2-$NaphtCH_2$	**14d** (82)	**15d** (76)	5 (c = 1.14, EtOH)
Bu	4-$BrPhCH_2$	**14e** (43)	**15e** (73)	7 (c = 1.06, EtOH)
Bu	2-$NaphtCH_2$	**14f** (41)	**15f** (65)	-3 (c = 0.90, EtOH)

[a] Compounds **14** gave correct elemental analysis.
[b] Compounds **15a**,**b**,**d**,**e** gave correct elemental analysis. Compound **15f** gave correct elemental analysis for C and N.

We have previously described a method for the preparation of enantiomerically pure (4*R*)-4-alkyl-3,4-dimethyl-2-pyrazolin-5-ones **17** from (−)-8-phenylmenthyl (2*R*)-2-alkyl-2-methylacetoacetates **16** (Table 4).[21] X-Ray diffraction studies on **16a** and **16b** showed *R* configuration at C-α. Accordingly, the new stereogenic center of **17a** and **17g** was also *R*. Compounds **8a**,**b**,**d**–**f** were converted into **17a**,**b**,**d**–**f** in excellent yields. Compound **17a** obtained from **8a** has the same $[\alpha]_D$ as the one obtained from **16a**. The configuration of **17b**,**d**–**f** was assigned by comparison of the circular dichroism with those of **17a** and **17g**. All of them presented a strong negative Cotton effect. Therefore, the major diastereoisomers obtained in the dialkylation process using D-ribonolactone acetonide as chiral auxiliary have *R* absolute

configuration at C-α, and consequently enantiopure hydrochlorides of (*S*)-α-alkylalanines, **15a**,**b**,**d**, and (*S*)-α-alkyl-α-butylglycines, **15e**,**f**, had been prepared.

Table 4
Preparation of enantiomerically pure 4,4-disubstituted 2-pyrazolin-5-ones **17**



16 (X_cH = (-)-8-phenylmenthol)
8 (X_cH = D-ribonolactone acetonide)

	R^1	R^2	products[a]	yield (%)	$[\alpha]_D$[b]
16a	CH_3	$PhCH_2$	**17a**[21]	95	-186 (c = 1.24)
16b	CH_3	4-$ClPhCH_2$	**17g**[21]	88	-87 (c = 0.12)
8a	CH_3	$PhCH_2$	**17a**	92	-180 (c = 1.20)
8b	CH_3	4-$BrPhCH_2$	**17b**	86	-144 (c = 1.01)
8d	CH_3	2-NaphtCH_2	**17d**	75	-211 (c = 0.88)
8e	Bu	4-$BrPhCH_2$	**17e**	74	-88 (c = 1.04)
8f	Bu	2-NaphtCH_2	**17f**	70	-127 (c = 1.01)

[a] Compounds **17d,e** gave correct elemental analysis. Compound **17b** and **17f** gave good HRMS.
[b] All determined in $CHCl_3$.

In conclusion, we have developed a new simple method for the synthesis of enantiopure (*S*)-α,α-disubstituted glycines using D-ribonolactone acetonide as a chiral auxiliary. The advantages of this approach are: (a) the facility to obtain the chiral auxiliary (only protection of available material is needed); (b) the fact that only one diastereomeric separation is needed (classical column chromatography); and (c) the method allows the introduction of substituents bulkier than methyl.

3. Experimental

Melting points were determined with a Kofler Reichert apparatus and are uncorrected. Infrared spectra were obtained on a Nicolet FT-IR 510 ZDX spectrophotometer. Proton and carbon magnetic resonance spectra were recorded on a Bruker AC250 spectrometer using tetramethylsilane as internal standard. Mass spectra were determined under electron impact at 70 eV. High resolution mass spectra were registered in the Servicio de Espectrometría de Masas de la Universidad de Córdoba. Optical rotations were recorded on a Propol polarimeter and circular dichroism on a Jasco J-715 apparatus.

3.1. 2,3-O-Isopropylidene-γ-D-ribonolactone 2-methylacetoacetate ***6***

A solution of **3** (5.00 g, 26.5 mmol) and 2,2,6-trimethyl-1,3-dioxen-4-one **5** (4.15 g, 29.2 mmol) in toluene (50 mL) was heated under reflux for 24 h. The solvent was evaporated and diethyl ether was added to the residue. The insoluble white solid was filtered off yielding 2,3-*O*-isopropylidene-γ-D-ribonolactone acetoacetate (5.92 g, 82%); mp 62–63°C; $[\alpha]_D$=−42 (c=1.04, acetone); IR (KBr, cm^{-1}) 2993, 2938, 1791, 1724; ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.38 (s, 3H), 1.46 (s, 3H), 2.24 (s, 3H), 3.49 (s, 2H), 4.38 (dq, J=12.5 and J=2.9 Hz, 2H), 4.73–4.76 (m, 3H). Enol form: 1.98 (s), 4.97 (s), 11.72 (s); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 25.4, 25.5, 30.3, 49.6, 64.0, 75.0, 77.6, 79.6, 113.7, 166.0, 173.5, 200.0. Anal. calcd for $C_{12}H_{16}O_7$: C, 52.94; H, 5.92. Found: C, 53.18; H, 5.95.

Methyl iodide was added (3.39 g, 23.9 mmol) to a magnetically stirred mixture of 2,3-*O*-isopropylidene-γ-D-ribonolactone acetoacetate (5.00 g, 18.4 mmol) and potassium carbonate (2.78 g, 20.2 mmol) in anhydrous acetone (50 mL). The mixture was heated at 40°C for 7 h, then it was filtered and the solvent from the filtrate was evaporated. The oil residue was chromatographed on silica gel under pressure, eluting with mixtures of increasing polarity of hexanes–ethyl acetate. Compound **6** (diastereomeric mixture) was obtained as a white solid (3.74 g, 71%); IR (KBr, cm^{-1}) 2994, 2952, 1783, 1755, 1715, 1244, 1075; ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.36 (d, J=7.3 Hz, 3H+3H), 1.40 (s, 3H+3H), 1.48 (s, 3H+3H), 2.23 (s, 3H), 2.25 (s, 3H), 3.54 (q, J=7.1 Hz, 1H), 3.55 (q, J=7.1 Hz, 1H), 4.30–4.48 (m, 2H+2H), 4.70–4.79 (m, 3H+3H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 12.8, 12.9, 25.4, 26.6, 28.2, 28.4, 53.2, 64.0, 64.1, 75.0, 77.5, 79.4, 79.7, 113.8, 169.2, 169.4, 173.2, 173.3, 203.0, 203.7. Anal. calcd for $C_{13}H_{18}O_7$: C, 54.54; H, 6.34. Found: C, 54.55; H, 6.54.

*3.2. 2,3-*O*-Cyclohexylidene-γ-D-ribonolactone 2-methylacetoacetate* **7**

Prepared as described for compound **6**.

2,3-*O*-Cyclohexylidene-γ-D-ribonolactone acetoacetate was obtained in 74% yield as a white solid, mp 82–83°C; $[\alpha]_D$=−53 (c=0.99, $CHCl_3$); IR (KBr, cm^{-1}) 2945, 2861, 1785, 1757, 1722, 1173, 1117; ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.40–1.67 (m, 10H), 2.26 (s, 3H), 3.51 (s, 3H), 4.41 (dq, J=12.1 and J=2.6 Hz, 2H), 4.73–4.76 (m, 3H). Enol form: 1.98 (s), 4.95 (s), 11.72 (s); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 23.6, 23.7, 24.6, 30.3, 34.8, 36.2, 49.5, 64.0, 74.7, 77.1, 79.7, 114.5, 165.9, 173.6, 199.9. Enol form: 21.2, 62.6, 88.6, 177.5. Anal. calcd for $C_{15}H_{20}O_7$: C, 57.69; H, 6.45. Found: C, 57.76; H, 6.52.

2,3-*O*-Cyclohexylidene-γ-D-ribonolactone 2-methylacetoacetate **7** was obtained as a diastereomeric mixture in 69% yield as a white solid; IR (KBr, cm^{-1}) 2938, 2854, 1785, 1750, 1715, 1166, 1117; ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.36 (d, J=7.3 Hz, 3H), 1.39 (d, J=6.6 Hz, 3H), 1.60–1.66 (m, 10H), 2.22 (s, 3H), 2.24 (s, 3H), 3.50 (q, J=7.3 Hz, 1H), 3.53 (q, J=7.3 Hz, 1H), 4.28–4.47 (m, 2H), 4.68–4.79 (m, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 12.8, 12.9, 23.6, 23.7, 24.7, 28.3, 28.4, 34.8, 34.9, 36.2, 53.2, 53.6, 64.0, 64.1, 74.7, 77.1, 79.6, 79.8, 114.6, 169.2, 169.4, 173.4, 173.5, 202.9, 203.7. Anal. calcd for $C_{16}H_{22}O_7$: C, 58.89; H, 6.79. Found: C, 58.68; H, 6.62.

*3.3. 2,3-*O*-Isopropylidene-γ-D-ribonolactone 2-butylacetoacetate* ***12***

2,3-*O*-Isopropylidene-γ-D-ribonolactone acetoacetate (5.00 g, 18.4 mmol) in anhydrous THF (12 mL) was added to magnetically stirred NaH (60% suspension in mineral oil, 0.81 g, 20.2 mmol) in anhydrous THF (10 mL) at room temperature and under nitrogen atmosphere. The reaction mixture was stirred for 15 min, then a solution of butyl iodide (8.3 mL, 73.5 mmol) in anhydrous THF (10 mL) was added. The mixture was heated under reflux for 24 h. THF was evaporated, and the residue partitioned between CH_2Cl_2 and H_2O. The aqueous layer was washed with CH_2Cl_2 (3×20 mL). The combined dichloromethane extracts were dried with anhydrous sodium sulfate and the solvent was evaporated to give a crude, which was chromatographed on silica gel under pressure, eluting with hexanes–diethyl ether mixtures of increasing polarity to afford 4.32 g (71%) of a diastereomeric mixture of **12** as an oil; IR (film, cm^{-1}) 2959, 2938, 2868, 1792, 1750, 1715, 1152, 1082; ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.90 (m, 3H+3H), 1.21–1.38 (m, 4H+4H), 1.40 (s, 3H+3H), 1.48 (s, 3H+3H), 1.77–1.89 (m, 2H+2H), 2.21 (s, 3H), 2.24 (s, 3H), 3.44 (t, J=7.3 Hz, 1H), 3.46 (t, J=7.3 Hz, 1H), 4.29–4.46 (m, 2H+2H), 4.68–4.82 (m, 3H+3H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 13.6, 22.2, 22.3, 25.4, 26.6, 27.9, 28.0, 28.8, 28.9, 29.5, 59.4, 59.8, 63.9, 64.0, 75.0, 77.6, 79.4, 79.6, 113.8, 168.7, 168.8, 173.2, 173.3, 202.6, 203.2.

3.4. 2,3-O-Isopropylidene-γ-D-ribonolactone (2R)-2-benzyl-2-methylacetoacetate **8a**+**9a**. General procedure for diastereoselective alkylation of compounds **6**, **7**, and **12**

Compound **6** (4.65 g, 16.2 mmol) in anhydrous THF (12 mL) was added to magnetically stirred NaH (60% suspension in mineral oil, 0.84 g (21.1 mmol)) in anhydrous THF (10 mL) at room temperature and under nitrogen atmosphere. The reaction mixture was stirred for 15 min, cooled down to −78°C and then a solution of benzyl bromide (4.17 g, 24.2 mmol) in anhydrous THF (10 mL) was added. The reaction was allowed to warm to room temperature and was stirred for 12 h. THF was evaporated, and the residue partitioned between CH_2Cl_2 and H_2O. The aqueous layer was washed with CH_2Cl_2 (3×20 mL). The combined dichloromethane extracts were dried with anhydrous sodium sulfate and the solvent was evaporated to give a crude which was a mixture of **8a** and **9a** in a ratio ca. 75:25 determined by integration of the ^{1}H NMR signal of the C*H*$_3$CO protons at δ 2.10 and 2.19. The crude was chromatographed on silica gel under pressure, eluting with hexanes–diethyl ether mixtures of increasing polarity to afford 2.81 g (46%) of **8a** and 1.04 g (17%) of **9a**. Compound **8a**: white solid; mp 101–103°C; $[\alpha]_D$=16 (c=1.09, $CHCl_3$); IR (KBr, cm^{-1}) 1785, 1729, 1715; ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.23 (s, 3H), 1.29 (s, 3H), 1.37 (s, 3H), 2.11 (s, 3H), 2.90 (d, J=13.1 Hz, 1H), 3.17 (d, J=13.1 Hz, 1H), 4.20–4.36 (m, 4H), 4.70 (t, J=2.2 Hz, 1H), 7.06–7.27 (m, 5H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 19.9, 25.5, 26.6, 26.7, 41.0, 61.1, 64.2, 74.9, 77.5, 79.1, 113.6, 127.0, 128.3 (2C), 130.1 (2C), 136.2, 171.3, 173.1, 204.9. Anal. calcd for $C_{20}H_{24}O_7$: C, 63.82; H, 6.43. Found: C, 63.70; H, 6.48. Compound **9a**: white solid; mp 67–68°C; $[\alpha]_D$=−39 (c=1.03, $CHCl_3$); IR (KBr, cm^{-1}) 1792, 1750, 1715; ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.37 (s, 3H), 1.38 (s, 3H), 1.44 (s, 3H), 2.10 (s, 3H), 2.94 (d, J=13.1 Hz, 1H), 3.31 (d, J=13.1 Hz, 1H), 4.07 (dd, J=12.4 and 2.7 Hz, 1H), 4.16 (d, J=5.8 Hz, 1H), 4.36 (dd, J=12.4 and 2.7 Hz, 1H), 4.44 (d, J=5.8 Hz, 1H), 4.67 (t, J=2.7 Hz, 1H), 7.12–7.22 (m, 5H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 18.5, 25.4, 26.3, 26.5, 40.8, 61.0, 64.2, 74.9, 77.5, 79.2, 113.7, 127.1, 128.4 (2C), 130.0 (2C), 135.8, 171.3, 173.1, 204.7. Anal. calcd for $C_{20}H_{24}O_7$: C, 63.82; H, 6.43. Found: C, 63.86; H, 6.55.

3.5. 2,3-O-Isopropylidene-γ-D-ribonolactone (2R)-2-(4-bromobenzyl)-2-methylacetoacetate **8b**

Prepared as for **8a** as a white solid (38% yield), mp 94–95°C (hexanes–diethyl ether); $[\alpha]_D$=−13 (c=1.06, $CHCl_3$); IR (KBr, cm^{-1}) 2987, 2938, 1778, 1757, 1708, 1173, 1103; ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.30 (s, 3H), 1.39 (s, 3H), 1.47 (s, 3H), 2.18 (s, 3H), 2.95 (d, J=13.9 Hz, 1H), 3.18 (d, J=13.9 Hz, 1H), 4.20–4.52 (m, 4H), 4.74 (t, J=2.2 Hz, 1H), 6.96 (d, J=8.4 Hz, 2H), 7.41 (d, J=8.4 Hz, 2H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 18.6, 25.5, 26.4, 26.6, 40.1, 60.9, 64.4, 75.0, 77.5, 79.3, 114.0, 121.3, 131.6 (2C), 131.8 (2C), 134.8, 171.1, 173.0, 204.4. Anal. calcd for $C_{20}H_{23}O_7Br$: C, 52.76; H, 5.09. Found: C, 52.69; H, 5.09.

3.6. 2,3-O-Isopropylidene-γ-D-ribonolactone (2S)-2-(4-bromobenzyl)-2-methylacetoacetate **9b**

Prepared as for **8a** as a white solid (16% yield), mp 95–96°C (hexanes–diethyl ether); $[\alpha]_D$=−43 (c=0.98, $CHCl_3$); IR (KBr, cm^{-1}) 2987, 2938, 1792, 1750, 1715, 1173, 1082; ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.37 (s, 3H), 1.40 (s, 3H), 1.45 (s, 3H), 2.11 (s, 3H), 2.91 (d, J=13.9 Hz, 1H), 3.25 (d, J=13.9 Hz, 1H), 4.09 (dd, J=12.4 and 2.4 Hz, 1H), 4.22 (d, J=5.4 Hz, 1H), 4.37 (dd, J=12.4 and 2.4 Hz, 1H), 4.48 (d, J=5.4 Hz, 1H), 4.69 (t, J=2.4 Hz, 1H), 7.03 (d, J=6.5 Hz, 2H), 7.40 (d, J=6.5 Hz, 2H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 19.8, 25.5, 26.6, 29.6, 40.3, 60.8, 64.3, 74.8, 77.3, 79.1, 113.8, 121.1, 128.5, 131.4 (2C), 131.9 (2C), 135.1, 171.1, 173.1, 204.7. Anal. calcd for $C_{20}H_{23}O_7Br$: C, 52.76; H, 5.09. Found: C, 52.89; H, 5.13.

3.7. 2,3-O-Isopropylidene-γ-D-ribonolactone 2-cinnamyl-2-methylacetoacetate **8c**+**9c**

Prepared as for **8a** as a mixture of diastereoisomers (71% yield); IR (KBr, cm^{-1}) 2987, 2945, 1792, 1750, 1715, 1216, 1173, 1082; ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.34 (s, 3H), 1.35 (s, 3H), 1.41 (s, 3H+3H), 1.46 (s, 3H), 1.47 (s, 3H), 2.16 (s, 3H), 2.18 (s, 3H), 2.59–2.80 (m, 2H+2H), 4.20–4.46 (m, 2H+2H), 4.57–4.77 (m, 3H+3H), 5.92–6.12 (m, 1H+1H), 6.44 (d, J=15.3 Hz, 1H), 6.46 (d, J=15.3 Hz, 1H), 7.21–7.34 (m, 5H+5H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 18.9, 19.4, 25.4, 26.1, 26.3, 26.6, 38.5, 39.0, 60.2, 64.3, 64.4, 75.0, 77.5, 79.4, 79.5, 113.8, 122.8, 123.6, 126.2, 127.6, 128.5, 134.3, 134.8, 136.6, 171.4, 173.2, 204.7, 204.9. Anal. calcd for $C_{22}H_{26}O_7$: C, 65.66; H, 6.51. Found: C, 65.70; H, 6.51.

3.8. 2,3-O-Isopropylidene-γ-D-ribonolactone (2R)-2-methyl-2-(2-naphthylmethyl)acetoacetate **8d**

Prepared as for **8a** as a white solid (47% yield), mp 108–109°C (hexanes–diethyl ether); $[\alpha]_D$=6 (c=1.01, $CHCl_3$); IR (KBr, cm^{-1}) 2996, 2965, 1788, 1735, 1216, 1083; ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.12 (s, 3H), 1.36 (s, 3H), 1.39 (s, 3H), 2.21 (s, 3H), 3.14 (d, J=13.5 Hz, 1H), 3.41 (d, J=13.5 Hz, 1H), 4.00–4.33 (m, 4H), 4.66 (t, J=2.2 Hz, 1H), 7.17–7.21 (m, 1H), 7.42–7.54 (m, 3H), 7.76–7.82 (m, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 18.7, 25.2, 26.4, 26.6, 41.0, 61.3, 64.4, 74.9, 75.0, 79.2, 113.7, 126.0, 126.4, 127.5, 127.6, 128.0, 128.1, 128.8, 132.3, 133.3, 133.4, 171.4, 173.1, 204.7. Anal. calcd for $C_{24}H_{26}O_7$: C, 67.59; H, 6.15. Found: C, 67.45; H, 6.22.

3.9. 2,3-O-Isopropylidene-γ-D-ribonolactone (2S)-2-methyl-2-(2-naphthylmethyl)acetoacetate **9d**

Prepared as for **8a** as a white solid (12% yield), mp 105–107°C (hexanes–diethyl ether); $[\alpha]_D$=−47 (c=1.06, $CHCl_3$); IR (KBr, cm^{-1}) 2966, 2938, 1799, 1750, 1715, 1159, 1082; ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.19 (s, 3H), 1.39 (s, 3H), 1.45 (s, 3H), 2.12 (s, 3H), 3.11 (d, J=13.9 Hz, 1H), 3.48 (d, J=13.9 Hz, 1H), 3.93 (d, J=5.4 Hz, 1H), 4.05 (dd, J=12.4 and 2.6 Hz, 1H), 4.34 (dd, J=12.4 and 2.6 Hz, 1H), 4.37 (d, J=5.4 Hz, 1H), 4.61 (t, J=2.6 Hz, 1H), 7.24–7.28 (m, 1H), 7.44–7.48 (m, 2H), 7.62 (s, 1H), 7.74–7.82 (m, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 20.2, 25.4, 26.6, 26.8, 41.2, 61.3, 64.3, 74.8, 77.3, 79.1, 113.7, 126.0, 126.4, 127.6 (2C), 127.8, 128.2, 129.0, 132.3, 133.3, 133.8, 171.5, 173.1, 205.0. Anal. calcd for $C_{24}H_{26}O_7$: C, 67.59; H, 6.15. Found: C, 67.55; H, 6.15.

3.10. 2,3-O-Isopropylidene-γ-D-ribonolactone (2R)-2-(4-bromobenzyl)-2-butylacetoacetate **8e**

Prepared as for **8a** as a white solid (44% yield), mp 64–65°C (pentane–diethyl ether); $[\alpha]_D$=6 (c=1.06, $CHCl_3$); IR (KBr, cm^{-1}) 2994, 2952, 2875, 1785, 1757, 1715, 1187, 1110; ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.92 (t, J=7.3 Hz, 3H), 1.02–1.36 (m, 4H), 1.39 (s, 3H), 1.47 (s, 3H), 1.79 (m, 2H), 2.13 (s, 3H), 3.04 (d, J=13.8 Hz, 1H), 3.11 (d, J=13.8 Hz, 1H), 4.18 (dd, J=12.4 and J=2.9 Hz, 1H), 4.26–4.33 (m, 1H), 4.32 (d, J=5.8 Hz, 1H), 4.48 (d, J=5.8 Hz, 1H), 4.73 (t, J=2.9 Hz, 1H), 6.88–6.92 (m, 2H), 7.38–7.43 (m, 2H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 13.7, 22.9, 25.5, 26.1, 26.6, 27.1, 30.8, 37.1, 64.4, 64.8, 75.0, 77.5, 79.2, 114.0, 121.3, 131.4 (2C), 131.6 (2C), 135.0, 170.9, 173.0, 204.1. Anal. calcd for $C_{23}H_{29}O_7Br$: C, 55.54; H, 5.88. Found: C, 55.53; H, 6.07.

3.11. 2,3-O-Isopropylidene-γ-D-ribonolactone (2S)-2-(4-bromobenzyl)-2-butylacetoacetate **9e**

Prepared as for **8a** as a white solid (15% yield), mp 72–74°C (pentane–diethyl ether); $[\alpha]_D$=−29 (c=1.12, $CHCl_3$); IR (KBr, cm^{-1}) 2987, 2959, 2924, 2868, 1785, 1764, 1715, 1159, 1075; ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.92 (t, J=6.9 Hz, 3H), 0.99–1.12 (m, 2H), 1.17–1.36 (m, 2H), 1.39 (s, 3H), 1.44

(s, 3H), 1.86–1.93 (m, 3H), 2.04 (s, 3H), 2.83 (d, J=13.5 Hz, 1H), 3.32 (d, J=13.5 Hz, 1H), 3.93–4.00 (m, 2H), 4.30–4.39 (m, 2H), 4.64 (t, J=2.2 Hz, 1H), 7.02 (d, J=8.0 Hz, 2H), 7.40 (d, J=8.0 Hz, 2H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 13.8, 22.9, 25.6, 25.8, 26.7, 27.3, 33.2, 37.7, 64.3, 65.1, 74.9, 77.5, 79.0, 113.8, 121.1, 131.5 (2C), 131.8 (2C), 135.7, 171.0, 173.1, 204.5. Anal. calcd for $C_{23}H_{29}O_7Br$: C, 55.54; H, 5.88. Found: C, 55.59; H, 6.06.

3.12. 2,3-O-Isopropylidene-γ-D-ribonolactone (2R)-2-butyl-2-(2-naphthylmethyl)acetoacetate ***8f***

Prepared as for **8a** as a white solid (47% yield), mp 38–40°C (hexanes–diethyl ether); $[\alpha]_D$=−4 (c=1.01, $CHCl_3$); IR (KBr, cm^{-1}) 2959, 2868, 1792, 1750, 1715, 1180, 1152, 1082; ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.94 (t, J=7.3 Hz, 3H), 1.11 (s, 3H), 1.38 (s, 3H), 1.11–1.38 (m, 4H), 1.69–1.88 (m, 2H), 2.15 (s, 3H), 3.29 (AB, J=13.9 Hz, 2H), 3.91 (d, J=5.8 Hz, 1H), 4.12 (dd, J=12.4 and J=2.5 Hz, 1H), 4.24 (d, J=5.8 Hz, 1H), 4.26 (dd, J=12.4 and J=2.5 Hz, 1H), 4.64 (t, J=2.5 Hz, 1H), 7.12–7.16 (m, 1H), 7.41–7.49 (m, 3H), 7.75–7.81 (m, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 13.7, 22.9, 25.2, 26.0, 26.5, 27.1, 30.8, 37.8, 64.3, 65.1, 74.8, 77.4, 79.1, 113.7, 126.0, 126.4, 127.5, 127.6, 127.8, 128.0, 128.5, 132.3, 133.3, 133.5, 171.3, 173.0, 204.4. Anal. calcd for $C_{27}H_{32}O_7$: C, 69.21; H, 6.88. Found: C, 69.33; H, 6.72.

3.13. 2,3-O-Isopropylidene-γ-D-ribonolactone (2S)-2-butyl-2-(2-naphthylmethyl)acetoacetate ***9f***

Prepared as for **8a** as a white solid (7% yield), mp 112–114°C (hexanes–diethyl ether); $[\alpha]_D$=36 (c=1.15, $CHCl_3$); IR (KBr, cm^{-1}) 2959, 2868, 1792, 1736, 1708, 1237, 1089; ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.92 (t, J=7.3 Hz, 3H), 1.13 (s, 3H), 1.35 (s, 3H), 1.11–1.40 (m, 4H), 1.87–1.99 (m, 2H), 2.04 (s, 3H), 3.27 (AB, J=13.9 Hz, 2H), 3.66 (d, J=5.8 Hz, 1H), 3.89 (dd, J=11.7 and J=2.2 Hz, 1H), 4.27 (d, J=5.8 Hz, 1H), 4.28 (dd, J=11.7 and J=2.2 Hz, 1H), 4.52 (t, J=2.9 Hz, 1H), 7.25 (dd, J=8.7 and J=2.02 Hz, 1H), 7.39–7.48 (m, 2H), 7.60 (s, 1H), 7.76–7.79 (m, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 13.7, 22.8, 25.3, 25.8, 26.5, 27.3, 33.2, 38.3, 64.1, 65.3, 74.7, 77.1, 78.9, 113.4, 125.9, 126.3, 127.4 (2C), 127.7, 128.0, 128.7, 132.1, 133.2, 134.1, 171.1, 173.1, 204.6. Anal. calcd for $C_{27}H_{32}O_7$: C, 69.21; H, 6.88. Found: C, 69.20; H, 6.66.

3.14. 2,3-O-Cyclohexylidene-γ-D-ribonolactone 2-benzyl-2-methylacetoacetate ***10+11***

Prepared as for **8a** as a mixture of diastereoisomers; IR (KBr, cm^{-1}) 2938, 2861, 1785, 1743, 1722, 1124, 1110; ^{1}H NMR (250 MHz, $CDCl_3$) δ major diastereoisomer: 1.30 (s, 3H), 1.39–1.62 (M, 10H), 2.19 (s, 3H), 2.98 (d, J=13.8 Hz, 1H), 3.24 (d, J=13.8 Hz, 1H), 4.18–4.35 (M, 5H), 4.72 (t, J=2.9 Hz, 1H), 7.06–7.26 (M, 5H); ^{1}H NMR (250 MHz, $CDCl_3$) δ minor diastereoisomer: 1.38 (s, 3H), 1.52–1.61 (m, 10H), 2.10 (s, 3H), 2.93 (d, J=13.5 Hz, 1H), 3.31 (d, J=13.5 Hz, 1H), 4.07 (dd, J=12.4 and 2.2 Hz, 4H), 4.45 (d, J=5.8 Hz, 1H), 4.68 (t, J=2.2 Hz, 1H), 7.12–7.23 (m, 5H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 18.6, 19.9, 23.6, 23.8, 24.7, 26.4, 26.8, 34.9, 36.2, 40.8, 41.1, 61.1, 64.3, 74.7, 77.1, 79.3, 79.4, 114.5, 127.1, 127.2, 128.5, 130.1, 130.2, 135.9, 171.4, 173.3, 204.7. Anal. calcd for $C_{23}H_{28}O_7$: C, 66.33; H, 6.78. Found: C, 66.39; H, 6.80.

3.15. Ethyl (2R)-2-benzyl-2-methyl-3-oxobutanoate ***13a****. General procedure for transesterification reaction*

A solution of **8a** (1.00 g, 2.6 mmol) and $Ti(OEt)_4$ (1.21 g, 5.3 mmol) in ethanol (40 mL) was refluxed for 5 h. The solution was evaporated and the crude solid was purified by column chromatography on silica gel under pressure, eluting with a mixture of hexanes–ethyl acetate. Product **13a** was obtained

as a colorless oil (0.57 g, 92%): bp 125°C/0.07 mmHg; $[\alpha]_D$=66 (c=0.64, $CHCl_3$) (lit.[11,19] $[\alpha]_D$=62.5 (c=0.42, $CHCl_3$)); IR (film, cm^{-1}) 2994, 1743, 1715; ^1H NMR (250 MHz, $CDCl_3$) δ 1.25 (t, J=6.6 Hz, 3H), 1.29 (s, 3H), 2.17 (s, 3H), 3.05 (d, J=13.9 Hz, 1H), 3.27 (d, J=13.9 Hz, 1H), 4.18 (m, 2H), 7.06–7.27 (m, 5H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 13.9, 18.9, 26.4, 40.3, 60.7, 61.3, 126.8, 128.2 (2C), 130.1 (2C), 136.4, 172.3, 205.3. Anal. calcd for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74. Found: C, 71.89; H, 7.95.

*3.16. Ethyl (2*R*)-2-(4-bromobenzyl)-2-methyl-3-oxobutanoate* ***13b***

Prepared as for **13a** (90% yield); bp 150°C/0.07 mmHg; $[\alpha]_D$=61 (c=1.12, $CHCl_3$); IR (film, cm^{-1}) 2987, 2938, 1729, 1715, 1180, 1110; ^1H NMR (250 MHz, $CDCl_3$) δ 1.25 (t, J=7.3 Hz, 3H), 1.28 (s, 3H), 2.16 (s, 3H), 2.99 (d, J=13.9 Hz, 1H), 3.22 (d, J=13.9 Hz, 1H), 4.18 (dq, J=7.3 Hz and J=3.3 Hz, 2H), 6.96–7.00 (m, 2H), 7.35–7.39 (m, 2H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 13.9, 19.0, 26.4, 39.8, 60.6, 61.5, 120.8, 131.3 (2C), 131.8 (2C), 135.5, 172.1, 205.0. Anal. calcd for $C_{14}H_{17}BrO_3$: C, 53.69; H, 5.47. Found: C, 53.75; H, 5.51.

*3.17. Ethyl (2*R*)-2-methyl-2-(naphthylmethyl)-3-oxobutanoate* ***13d***

Prepared as for **13a** (93% yield); bp 175°C/0.07 mmHg; $[\alpha]_D$=57 (c=1.27, $CHCl_3$); IR (film, cm^{-1}) 3058, 2980, 2938, 1743, 1715, 1223, 1187, 1096; ^1H NMR (250 MHz, $CDCl_3$) δ 1.24 (t, J=6.9 Hz, 3H), 1.33 (s, 3H), 2.19 (s, 3H), 3.21 (d, J=13.1 Hz, 1H), 3.44 (d, J=13.1 Hz, 1H), 4.19 (q, J=6.9 Hz, 2H), 7.19–7.25 (m, 1H), 7.40–7.47 (m, 2H), 7.56 (s, 1H), 7.71–7.80 (m, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 14.0, 19.1, 26.5, 40.5, 60.9, 61.4, 125.6, 126.0, 127.5 (2), 127.7, 128.3, 128.9, 132.3, 133.3, 134.1, 172.4, 205.4. Anal. calcd for $C_{18}H_{20}O_3$: C, 76.03; H, 7.09. Found: C, 75.89; H, 7.26.

*3.18. Ethyl (2*R*)-2-(4-bromobenzyl)-2-butyl-3-oxobutanoate* ***13e***

Prepared as for **13a** (reaction time 48 h, 37% yield); bp 150°C/0.07 mmHg; $[\alpha]_D$=33 (c=1.10, $CHCl_3$); IR (film, cm^{-1}) 2959, 2931, 2868, 1736, 1715, 1194; ^1H NMR (250 MHz, $CDCl_3$) δ 0.90 (t, J=6.9 Hz, 3H), 0.96–1.42 (m, 7H), 1.69–1.87 (m, 2H), 2.10 (s, 3H), 3.05 (d, J=14.2 Hz, 1H), 3.18 (d, J=14.2 Hz, 1H), 4.08–4.25 (m, 2H), 6.90 (d, J=2.9 Hz, 2H), 6.95 (d, J=2.9 Hz, 2H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 13.8, 13.9, 22.9, 25.9, 27.1, 31.1, 36.6, 61.3, 64.5, 120.7, 131.3 (2C), 131.5 (2C), 135.6, 171.8, 204.8. Anal. calcd for $C_{17}H_{23}O_3Br$: C, 57.47; H, 6.53. Found: C, 57.79; H, 6.46.

*3.19. Ethyl (2*R*)-2-butyl-2-(2-naphthylmethyl)-3-oxobutanoate* ***13f***

Prepared as for **13a** (reaction time 48 h, 49% yield); $[\alpha]_D$=32 (c=1.50, $CHCl_3$); IR (film, cm^{-1}) 3058, 2959, 2931, 2868, 1736, 1715, 1187; ^1H NMR (250 MHz, $CDCl_3$) δ 0.84 (t, J=7.3 Hz, 3H), 1.14 (t, J=7.3 Hz, 3H), 1.09–1.28 (m, 4H), 1.70–1.82 (m, 2H), 2.04 (s, 3H), 3.26 (AB, J=13.9 Hz, 2H), 3.99–4.18 (m, 2H), 7.07–7.12 (m, 2H), 7.31–7.39 (m, 2H), 7.44 (s, 1H), 7.63–7.72 (m, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 13.9, 14.0, 22.9, 26.1, 27.2, 31.2, 37.4, 61.2, 64.9, 125.6, 126.0, 127.5 (2C), 127.8, 128.0, 128.6, 132.3, 133.3, 134.2, 172.1, 205.2. Anal. calcd for $C_{21}H_{26}O_3$: C, 77.27; H, 8.03. Found: C, 76.91; H, 7.78.

*3.20. Ethyl (2S)-2-acetylamino-2-methyl-3-naphthylpropanoate **14d**. General procedure for Schmidt rearrangement*

Methanesulfonic acid (5.8 mL) was added dropwise to a stirred mixture of ketoester **13d** (1.30 g, 4.6 mmol) and DME (5 mL) cooled at −30°C. Sodium azide (0.89 g, 13.7 mmol) was then added portionwise. When the evolution of nitrogen ceased the mixture was left at room temperature for 24 h. More DME (10 mL) and 30% aqueous ammonia were added until pH ca. 9. The mixture was partitioned between dichloromethane and water. The organic layer was dried and evaporated. The residue was purified through silica gel eluting with hexanes–ethyl acetate mixtures of increasing polarity to afford **14d** (1.13 g, 82%) as an oil: bp 200°C/0.07 mmHg; $[\alpha]_D$=51 (c=0.97, $CHCl_3$); IR (film, cm^{-1}) 3290, 1736, 1652; ^1H NMR (250 MHz, $CDCl_3$) δ 1.24 (t, J=7.3 Hz, 3H), 1.60 (s, 3H), 1.86 (s, 3H), 3.28 (d, J=13.8 Hz, 1H), 3.56 (d, J=13.8 Hz, 1H), 4.15 (q, J=7.3 Hz, 2H), 6.10 (broad s, 1H), 7.07–7.11 (m, 1H), 7.33–7.39 (m, 2H), 7.43 (s, 1H), 7.62–7.72 (m, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 14.1, 23.4, 23.9, 40.9, 61.1, 61.8, 125.6, 125.9, 127.5 (2C), 128.0, 128.6, 132.3, 133.3, 134.1, 169.6, 173.9. Anal. calcd for $C_{18}H_{21}NO_3$: C, 72.22; H, 7.07; N, 4.68. Found: C, 71.81; H, 7.34; N, 4.33.

*3.21. Ethyl (2S)-2-acetylamino-2-methyl-3-phenylpropanoate **14a***

Prepared as for **14d** (82% yield); colorless oil, bp 175°C/0.07 mmHg; $[\alpha]_D$=53 (c=1.02, $CHCl_3$) (lit.[13b] $[\alpha]_D$=49 (c=0.56, $CHCl_3$)); IR (KBr, cm^{-1}) 3290, 3065, 3030, 2987, 2938, 1736, 1659, 1117; ^1H NMR (250 MHz, $CDCl_3$) δ 1.32 (t, J=7.3 Hz, 3H), 1.66 (s, 3H), 1.95 (s, 3H), 3.19 (d, J=13.5 Hz, 1H), 3.56 (d, J=13.5 Hz, 1H), 4.22 (dq, J=7.3 and J=3.3 Hz, 2H), 6.10 (broad s, 1H), 7.04–7.26 (m, 5H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 14.0, 23.2, 23.8, 40.8, 60.9, 61.6, 126.7, 128.0 (2C), 129.8 (2C), 136.5, 169.5, 173.8.

*3.22. Ethyl (2S)-2-acetylamino-3-(4-bromophenyl)-2-methylpropanoate **14b***

Prepared as for **14d** (63% yield); white solid, mp 69–71°C; $[\alpha]_D$=42 (c=0.95, $CHCl_3$); IR (KBr, cm^{-1}) 3459–3170, 3065, 2980, 2938, 1736, 1652, 1490, 1117; ^1H NMR (250 MHz, $CDCl_3$) δ 1.33 (t, J=7.3 Hz, 3H), 1.66 (s, 3H), 1.96 (s, 3H), 3.15 (d, J=13.1 Hz, 1H), 3.59 (d, J=13.1 Hz, 1H), 4.06–4.25 (m, 2H), 6.04 (broad s, 1H), 6.85 (d, J=8.04 Hz, 2H), 7.30 (d, J=8.04 Hz, 2H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 14.1, 23.4, 24.1, 40.1, 61.1, 61.9, 120.9, 131.3 (2C), 131.5 (2C), 135.7, 169.5, 173.7. Anal. calcd for $C_{14}H_{18}NO_3Br$: C, 51.23; H, 5.53; N, 4.27. Found: C, 51.34; H, 5.49; N, 4.27.

*3.23. Ethyl (2S)-2-acetylamino-2-(4-bromobenzyl)hexanoate **14e***

Prepared as for **14d** (43% yield); white solid, mp 88–89°C; $[\alpha]_D$=61 (c=1.15, $CHCl_3$); IR (KBr, cm^{-1}) 3268, 2959, 2952, 2869, 1736, 1637, 1208; ^1H NMR (250 MHz, $CDCl_3$) δ 0.88 (t, J=6.9 Hz, 3H), 0.88–1.00 (m, 1H), 1.16–1.37 (m, 3H), 1.34 (d, J=6.9 Hz, 3H), 1.71–1.88 (m, 1H), 1.97 (s, 3H), 2.61 (dt, J=12.8 and J=4.4 Hz, 1H), 3.03 (d, J=13.1 Hz, 1H), 3.74 (d, J=13.1 Hz, 1H), 4.13–4.34 (m, 2H), 6.19 (broad s, 1H), 6.90 (d, J=8.4 Hz, 2H), 7.35 (d, J=8.4 Hz, 2H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 13.9, 14.1, 22.4, 24.3, 26.4, 35.0, 39.8, 61.9, 65.8, 120.8, 131.3 (4C), 135.7, 169.3, 173.2. Anal. calcd for $C_{17}H_{24}BrNO_3$: C, 55.14; H, 6.53; N, 3.78. Found: C, 55.24; H, 6.53; N, 3.58.

*3.24. Ethyl (2S)-2-acetylamino-2-(2-naphthylmethyl)hexanoate **14f***

Prepared as for **14d** as a white solid (41% yield), mp 72–74°C; $[\alpha]_D$=83 (c=0.99, $CHCl_3$); IR (KBr, cm^{-1}) 3281, 3058, 2956, 2861, 1740, 1645, 1549, 1205; ^1H NMR (250 MHz, $CDCl_3$) δ 0.90 (t, J=7.3

Hz, 3H), 0.82–1.05 (m, 2H), 1.26–1.46 (m, 2H), 1.38 (t, J=7.3 Hz, 3H), 1.85–1.95 (m, 1H), 1.98 (s, 3H), 2.70 (dt, J=13.9 and 4.4 Hz, 1H), 3.60 (AB, J=13.2 Hz, 2H), 4.21–4.36 (m, 2H), 6.18 (s, 1H), 7.14–7.18 (m, 1H), 7.42–7.45 (m, 2H), 7.50 (s, 1H), 7.70–7.81 (m, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 13.9, 14.2, 22.5, 24.3, 26.5, 35.1, 40.6, 61.9, 66.2, 125.5, 125.9, 127.5 (3C), 127.9, 128.4, 132.4, 133.4, 134.3, 169.4, 173.5; Anal. calcd for $C_{21}H_{27}NO_3$: C, 73.87; H, 7.97; N, 4.10. Found: C, 73.82; H, 7.80; N, 4.05.

*3.25. (S)-α-Benzylalanine hydrochloride **15b**. General procedure for acid hydrolysis*

A mixture of 0.49 g of **14a** in 6 M HCl was heated at reflux for 24 h. After cooling at room temperature a precipitate was formed and filtered, yielding **15a** as a white solid (0.33 g, 81%); mp 160–164°C (d); $[\alpha]_D$=−7 (c=1.22, H_2O); IR (KBr, cm^{-1}) 3184–2446, 1736, 1237, 1194; ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.48 (s, 3H), 3.12 (s, 2H), 7.21–7.36 (m, 5H), 8.49 (s, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 21.9, 42.3, 59.9, 127.6, 128.7 (2C), 130.5 (2C), 134.1, 172.3. Anal. calcd for $C_{10}H_{14}ClNO_2$: C, 55.69; H, 6.54; N, 6.49. Found: C, 55.52; H, 6.62; N, 6.07.

*3.26. (S)-α-(4-Bromobenzyl)alanine hydrochloride **15b***

Prepared as for **15a** (81% yield) as a white solid; mp 161–163°C (d); $[\alpha]_D$=−8 (c=1.05, H_2O); IR (KBr, cm^{-1}) 3297–2671, 1757, 1511, 1490, 1173; ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.49 (s, 3H), 3.13 (s, 2H), 7.21 (d, J=8.0 Hz, 2H), 7.52 (d, J=8.0 Hz, 2H), 8.55 (s, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 22.1, 41.4, 59.7, 121.1, 131.5 (2C), 132.7 (2C), 133.5, 172.2. Anal. calcd for $C_{10}H_{13}BrClNO_2$: C, 40.77; H, 4.45; N, 4.75. Found: C, 40.60; H, 4.38; N, 4.52.

*3.27. (S)-α-(2-Naphthylmethyl)alanine hydrochloride **15d***

Prepared as for **15a** (76% yield) as a white solid; mp 170–174°C (d); $[\alpha]_D$=5 (c=1.14, EtOH); IR (KBr, cm^{-1}) 3395–2503, 1743, 1525, 1209; ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.56 (s, 3H), 3.32 (s, 2H), 7.37–7.40 (m, 1H), 7.47–7.54 (m, 2H), 7.79–7.92 (m, 4H), 8.59 (s, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 22.1, 42.4, 60.0, 126.2, 126.4, 127.7, 127.9, 128.1, 128.4, 129.4, 131.7, 132.5, 133.1, 172.4. Anal. calcd for $C_{14}H_{16}ClNO_2 \cdot H_2O$: C, 59.26; H, 6.39; N, 4.94. Found: C, 59.12; H, 6.46; N, 4.80.

*3.28. (S)-α-(4-Bromobenzyl)-α-butylglycine hydrochloride **15e***

Prepared as for **15a** (73% yield) as a white solid; mp 169–173°C (d); $[\alpha]_D$=7 (c=1.06, EtOH); IR (KBr, cm^{-1}) 3662–2347, 1722, 1511, 1209; ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.86 (t, J=7.0 Hz, 3H), 1.22–1.50 (m, 4H), 1.69–1.92 (m, 2H), 3.07 (d, J=14.2 Hz, 1H), 3.15 (d, J=14.2 Hz, 1H), 7.24 (d, J=8.0 Hz, 2H), 7.53 (d, J=8.0 Hz, 2H), 8.35 (s, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 13.8, 22.3, 25.0, 35.5, 40.3, 63.2, 121.1, 131.5 (2C), 133.0 (2C), 133.4, 171.8. Anal. calcd for $C_{13}H_{19}BrClNO_2 \cdot 1/2H_2O$: C, 45.16; H, 5.79; N, 4.05. Found: C, 44.88; H, 5.80; N, 3.94.

*3.29. (S)-α-Butyl-α-(2-naphthylmethyl)glycine hydrochloride **15f***

Prepared as for **15a** (65% yield) as a white solid; mp 110–112°C (d); $[\alpha]_D$=−3 (c=0.90, EtOH); IR (KBr, cm^{-1}) 3698–2341, 1729, 1511, 1216; ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.88 (t, J=6.9 Hz, 3H), 1.25–1.33 (m, 3H), 1.52–1.59 (m, 1H), 1.84–2.01 (m, 2H), 3.36 (s, 3H), 7.44–7.54 (m, 3H), 7.81–7.92 (m, 4H), 8.47 (s, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 14.6, 25.1, 25.9, 36.4, 42.1, 64.3, 126.8, 127.0,

128.4, 128.7, 129.5, 130.5, 132.5, 133.2, 133.8, 172.7. Anal. calcd for $C_{17}H_{22}ClNO_2 \cdot H_2O$: C, 62.66; N, 4.30. Found: C, 62.88; N, 4.59.

*3.30. (4R)-4-Benzyl-3,4-dimethyl-2-pyrazolin-5-one **17a**. General procedure for preparation of 2-pyrazolin-5-ones **17a**,**b**,**d**–**g***

A solution of 0.20 g (0.5 mmol) of **8a** and 0.27 g (5.3 mmol) of hydrazine hydrate in ethanol (8 mL) was heated at 140°C in a closed reactor for 24 h. After cooling at room temperature, the solvent was evaporated and the residue was chromatographed on silica gel under pressure with hexanes–ethyl acetate as eluent, to afford **17a** (0.10 g, 92%) as a white solid; mp 99–101°C (hexanes–diethyl ether); $[\alpha]_D$=−180 (c=1.20, $CHCl_3$) (lit.[15] $[\alpha]_D$=−186 (c=1.24, $CHCl_3$)); IR (KBr, cm^{-1}) 3163, 1708, 1666; ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.34 (s, 3H), 2.05 (s, 3H), 2.84 (d, J=13.8 Hz, 1H), 3.12 (d, J=13.8 Hz, 1H), 7.08–7.26 (m, 5H), 8.03 (s, 1H, NH); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 14.2, 20.3, 41.2, 53.5, 127.2–128.9 (5C), 135.3, 163.4, 179.6.

*3.31. (4R)-4-(4-Bromobenzyl)-3,4-dimethyl-2-pyrazolin-5-one **17b***

Prepared as for **17a** from **8b** as a white solid (86% yield); mp 52–54°C (hexanes–diethyl ether); $[\alpha]_D$=−144 (c=1.01, $CHCl_3$); IR (KBr, cm^{-1}) 3227, 2924, 2854, 1701; ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.33 (s, 3H), 2.04 (s, 3H), 2.78 (d, J=13.9 Hz, 1H), 3.05 (d, J=13.9 Hz, 1H), 6.97 (d, J=8.1 Hz, 2H), 7.34 (d, J=8.1 Hz, 2H), 8.16 (s, 1H, NH); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 14.1, 20.2, 40.4, 53.4, 121.3, 130.6, 131.5, 134.2, 163.0, 179.3. HRMS: calcd for $C_{12}H_{13}BrN_2O$: 280.0224 and 282.0207. Found: 280.0211 and 282.0191.

*3.32. (4R)-3,4-Dimethyl-4-(2-naphthylmethyl)-2-pyrazolin-5-one **17d***

Prepared as for **17a** from **8d** as a white solid (75% yield); mp 131–133°C (hexanes–diethyl ether); $[\alpha]_D$=−211 (c=0.88, $CHCl_3$); IR (KBr, cm^{-1}) 3191, 3093, 2973, 2917, 2840, 1708, 1680, 773; ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.40 (s, 3H), 2.09 (s, 3H), 3.00 (d, J=13.5 Hz, 1H), 3.30 (d, J=13.5 Hz, 1H), 7.21–7.26 (m, 1H), 7.42–7.48 (m, 2H), 7.57 (s, 1H), 7.69–7.79 (m, 3H), 7.92 (s, 1H, NH); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 14.3, 20.4, 41.3, 53.6, 125.8, 126.0, 127.1, 127.5, 127.8 (2C), 128.0, 132.5, 132.9, 133.3, 163.4, 179.6. Anal. calcd for $C_{16}H_{16}N_2O$: C, 76.16; H, 6.39; N, 11.10. Found: C, 76.08; H, 6.63; N, 11.07.

*3.33. (4R)-4-(4-Bromobenzyl)-4-butyl-3-methyl-2-pyrazolin-5-one **17e***

Prepared as for **17a** from **8e** as a white solid (74% yield); mp 133–135°C (pentane–diethyl ether); $[\alpha]_D$=−88 (c=1.04, $CHCl_3$); IR (KBr, cm^{-1}) 3198, 3086, 2959, 2931, 2861, 1701; ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.86 (t, J=7.3 Hz, 3H), 0.92–1.34 (m, 4H), 1.58–1.70 (m, 1H), 1.79–1.92 (m, 1H), 2.01 (s, 3H), 2.77 (d, J=13.5 Hz, 1H), 3.03 (d, J=13.5 Hz, 1H), 6.96 (d, J=8.0 Hz, 2H), 7.34 (d, J=8.0 Hz, 2H), 8.52 (s, 1H, NH); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 13.7, 14.4, 22.6, 26.2, 34.6, 40.3, 58.5, 121.2, 130.7, 131.4, 134.0, 162.0, 178.7; Anal. calcd for $C_{15}H_{19}BrN_2O$: C, 55.74; H, 5.92; N, 8.67. Found: C, 55.76; H, 5.70; N, 8.30.

3.34. (4R)-4-Butyl-3-methyl-4-(2-naphthylmethyl)-2-pyrazolin-5-one **17f**

Prepared as for **17a** from **8f** as a white solid (70% yield); mp 87–88°C (pentane–diethyl ether); $[\alpha]_D$=−127 (c=1.01, $CHCl_3$); IR (KBr, cm^{-1}) 3234, 3058, 2959, 2931, 2861, 1701; ^1H NMR (250 MHz, $CDCl_3$) δ 0.88 (t, J=7.3 Hz, 3H), 0.93–1.43 (m, 6H), 1.73 (dt, J=12.0 and J=4.3 Hz, 1H), 1.68 (dt, J=12.0 and J=4.3 Hz, 1H), 2.07 (s, 3H), 3.13 (AB, J=13.9 Hz, 2H), 7.21–7.25 (m, 1H), 7.41–7.45 (m, 3H), 7.90 (s, 1H, NH); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 13.7, 14.5, 22.6, 26.2, 34.7, 41.1, 58.6, 125.7, 125.9, 127.2, 127.5, 127.8, 127.9, 132.4, 132.7, 133.2, 162.3, 179.1. HRMS: calcd for $C_{19}H_{22}N_2O$: (M+1) 295.1796. Found: 295.1810.

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