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Isomannide and isosorbide as new chiral auxiliaries for the stereoselective synthesis of tertiary α-hydroxy acids

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Abstract—Isomannide and isosorbide are selectively protected to provide new chiral auxiliaries suitable for the preparation of enantiopure tertiary α-hydroxy acids. Diastereoselective additions of organozinc reagents on the derived phenylglyoxylates afford the desired α-hydroxy acids with 60–99% ee after saponification. Both absolute configurations of the α-hydroxy acids can be accessed, by adapted choice of either the starting diol or the protecting group.

1. Introduction

Chiral tertiary α-hydroxy acids constitute important building blocks[1a–c] and synthetic intermediates[2a,b] for the preparation of complex biologically active substances.[3] As a consequence, numerous studies have been devoted to their asymmetric synthesis during the last few years. They involve classical[4] diastereoselective additions of organometallics to α-keto esters bearing cyclohexane based chiral auxiliaries such as (i) (−)-menthol,[7a,b] (ii) 8-phenylmenthol,[8a,b] (iii) *chiro*-inositol derivatives[9] (iv) *trans*-2-phenylcyclohexanol[10] and the derived 2-nitroxy[11] and 2-aryloxy[12] analogues. To the best of our knowledge, the only alternate types of auxiliaries are 2′-substituted-1,1′-binaphtalenols,[13] 2,5-bis(methoxymethoxymethyl) pyrrolidine,[14] (dl) 2-hydroxyheptahelicene or secondary anthryl alcohols, and (−)-quinine.[15] However, their application has been restricted to the introduction of methyl and phenyl groups. In the first two examples, low selectivities were obtained when compared with generic auxiliaries. In the case of hydroxyhelicenes and anthryl alcohols, only diastereoisomeric mixtures of α-hydroxy esters were isolated due to the use of racemic auxiliaries. Therefore, (−)-quinine remains the uniquely interesting candidate, although reactions with other nucleophiles are needed to assess the scope and limitations.

2. Results and discussion

As a part of our efforts to develop chemical applications for starch industry by-products, isosorbide **1** and isomannide **2** are an attractive class of readily accessible chiral auxiliaries.[16a,b] In the present study, we illustrate their synthetic value through preparation of new mono-protected derivatives, and their application for the stereoselective synthesis of tertiary α-hydroxy acids.

As shown in previous reports,[16a,17] isosorbide **1** and isomannide **2** can be selectively mono-benzylated to afford *exo* or *endo* benzylated isosorbide **3** and **4**, and mono-benzylated isomannide **5**. In a preliminary phase of our work, the preparation of compounds **3** and **4** were optimized and the purification of the protected derivatives **3**–**5** simplified. Thus, *endo*-benzylated isosorbide **4** was prepared at room temperature instead of 90°C, which prevented degradation of the reaction mixture. Compounds **3**–**5** were then obtained as pure products by precipitation from cold Et_2O instead of flash chromatography. These improvements prompted us to articulate the synthesis of mono-methylated isosorbides **9**, **10** and isomannide **11** on the benzylated products **3**–**5** instead of the corresponding mono-acetates.[18] Thus, mono-benzylated intermediates **3**–**5** were converted quantitatively into compounds **6**–**8** in only 5 h by reaction with iodomethane under solvent free phase transfer catalysis (KOH, Aliquat 336). Hydrogenolysis performed on intermediates **6**–**8** for 2 h afforded the desired mono-methylated isosorbides **9**, **10** and, isomannide **11** in quantitative yields (Scheme 1).

As a consequence, the 48 h required for the preparation of the mono-acetates are now circumvented and compounds **9**–**11** are obtained through a straightforward sequence. The preparation of the chiral α-keto esters **12**–**18** as starting materials for the synthesis of the derived α-hydroxy acids was then achieved. The obtained mono-protected auxiliaries **3**–**5**, and **11** were converted in 55% to quantitative yield into the derived phenylglyoxylates **13**–**15**, **17**, **18** and pyruvates

Keywords: isosorbide; isomannide; α-hydroxy acids; asymmetric additions.
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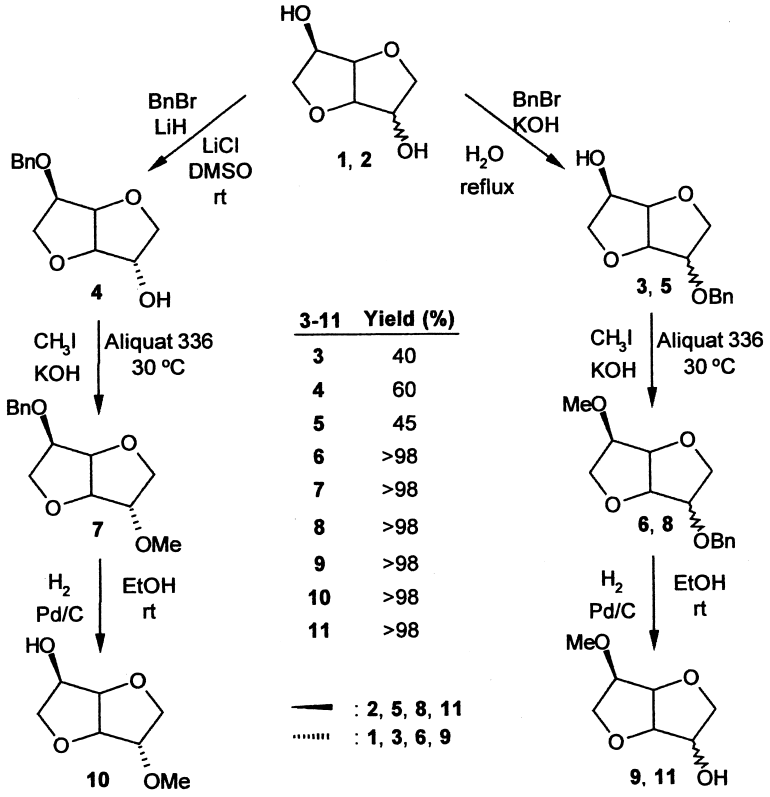


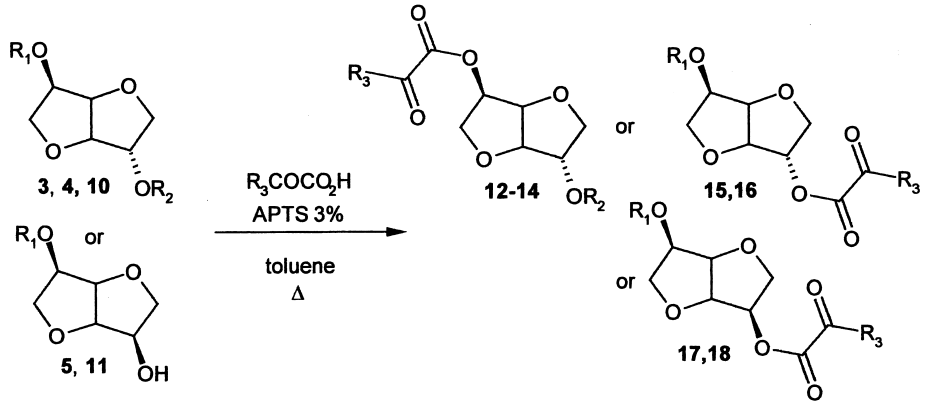
3-11	Yield (%)
3	40
4	60
5	45
6	>98
7	>98
8	>98
9	>98
10	>98
11	>98

Scheme 1.

12, **16** via azeotropic condensations with the corresponding α-keto acids (Scheme 2).

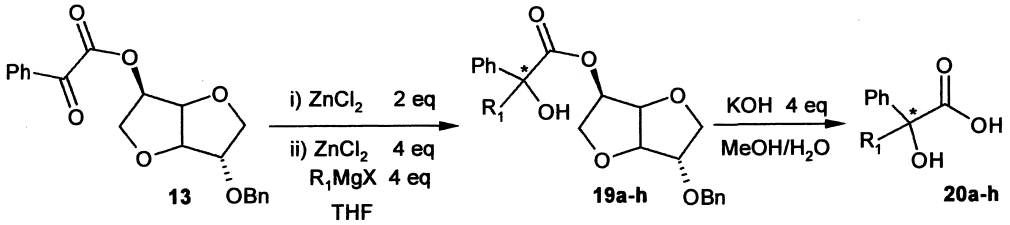
Interestingly, the phenylglyoxylate **13** was alternatively prepared in only 6 min under microwave irradiation in 80% yield, comparable with the use of classical heating conditions. In this case, no degradation of the dioxabicyclo[3.3.0]octane unit was observed, attesting to the compatibility of the isosorbide and isomannide derived auxiliaries under these reaction conditions.

We have then focused our work on condensations of



12-18	R_1	R_2	R_3	Yield (%)
12	/	Bn	Me	>98
13	/	Bn	Ph	95
14	/	Me	Ph	65
15	Bn	/	Ph	87
16	Bn	/	Me	70
17	Bn	/	Ph	55
18	Me	/	Ph	68

Scheme 2.



19,20	R_1	Yield (%)	d.e. (%)	e.e. (%)	Abs. Conf.
a	Et	65	97	94	(*R*)
b	iPr	78	88	82	(*R*)
c	nBu	75	92	89	(*R*)
d	iBu	48	65	60	(*R*)
e	tBu	27	60	/	(*R*)
f	All	50	10	10	(*R*)
g	cHex	62	92	90	(*R*)
h	Bn	58	72	/	(*R*)

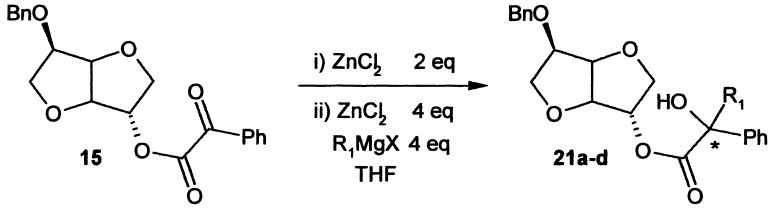
Scheme 3.

compounds **12**–**18** with various organometallic species. A first group of experiments was conducted with organozinc reagents, prepared in situ by reactions of Grignard reagents with zinc chloride.[7a] During the optimization of the reaction conditions, performed with a test set composed of compound **13** and EtMgCl, we found that the yield and stereoselectivity are strongly dependant on (i) the relative amounts of zinc chloride and the Grignard reagent, (ii) the temperature, and (iii) the way the electrophile and the nucleophile are added to each other.

Thus, we determined that adding 2 equiv. of $ZnCl_2$ and the α-keto ester, on a pre-reacted mixture of 4 equiv. of $ZnCl_2$ and of Grignard reagent at −20°C, lead to the best results. By pre-mixing 2 equiv. of $ZnCl_2$ with the α-keto ester before the introduction on the nucleophile, 1 equiv. is implicated in the precomplexation of the dicarbonyl moiety while the second is probably involved in the complexation of the two ethers oxygens of the bicyclic core. These conditions were then successfully applied to the condensation of other nucleophiles with compound **13** (entries a–e), although a decrease in temperature to −78°C was required to preserve a good degree of selectivity with less reactive derivatives (entries f–h) (Scheme 3).

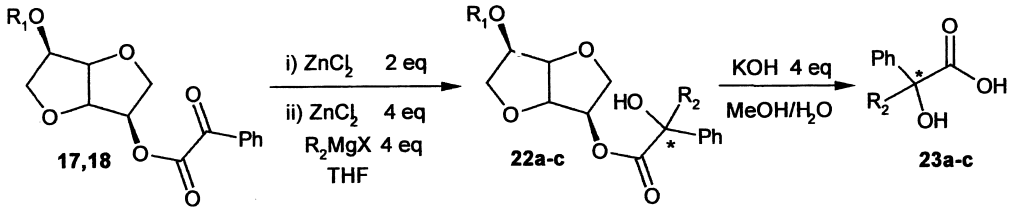
The α-hydroxy acids **20a**–**h** were obtained as (*R*) isomers in accordance with the Whitesell's model,[19] in comparable yields and diastereoselectivities when compared to classical auxiliaries.[12,7a] Attempts to introduce the particularly hindered *tert*-butyl group resulted in only 27% yield (entry e), while reaction with allylzinc chloride proceeded with low selectivity as previously reported (entry f).[20] In the later case however, introduction of an allyl group on compound **13** could be achieved in a more selective manner via a $SnCl_4$ mediated addition of trimethylallylsilane.[21] Thus, the desired α-hydroxy ester **19f** was isolated in 51% yield with an improved 65% de (72% ee for **20f** after saponification). As previously observed with the use of microwave irradiation, the chiral auxiliary showed excellent stability towards reactions performed in the presence of a strong Lewis acid.

In order to monitor the influence of protecting groups on the stereoselectivity of the reaction, an additional attempt was



21	R_1	Yield (%)	d.e. (%)
a	Et	48	14
b	iPr	51	12
c	nBu	65	20
d	All	25	27

Scheme 4.



22,23	R_1	R_2	Yield (%)	d.e. (%)	Abs. Conf.
a	Bn	iPr	53	>99	(*S*)
b	Bn	iBu	23	94	(*S*)
c	Me	iPr	70	81	(*R*)

Scheme 5.

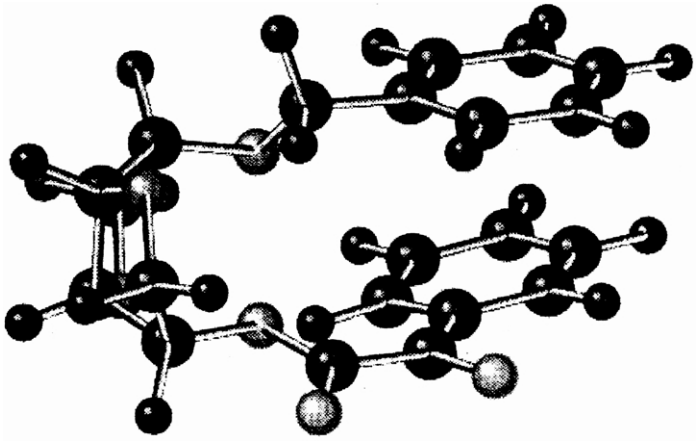
performed on *exo-O*-methylated compound **14** with *i*PrZnCl. In this case, no variation was observed. The desired substituted mandelic acid **20b** was isolated as the (*R*) isomer with equivalent diastereoselectivity and yield (90 and 50% respectively) as obtained from compound **13** (Scheme 3, entry b), suggesting that the protecting group does not participate to the induction. However a dramatic decrease in selectivity was observed by changing over the positions of the α-keto ester and of the protecting group. Therefore, additions of alkylzincs on compound **15** afforded the desired α-hydroxy esters **21a–d** in only 12–27% de (Scheme 4).

The present set of reactions suggests that a high level of stereo-induction can only be reached when the reactive center is located inside the 120° dihedral angle formed by the bicyclic skeleton. Since the protecting group cannot participate in the induction when placed on the opposite side of the molecule, a last series of reactions was performed on isomannide derived α-keto esters **17** and **18**. In this case, the reactive site and the protecting groups are both located into the cavity of the auxiliary (Scheme 5).

As observed with alkylations of α-keto ester **13**, the desired hydroxy esters **22a–c** are obtained with high stereoselectivity when prepared from compounds **17** and **18**. Remarkably, both absolute configurations of the asymmetric center created can be selectively obtained by an adapted choice of the protecting group (Scheme 5, entries a and c). However, by placing the benzyl protecting group in close contact with the reactive center, selective introduction of nucleophiles is enhanced. Thus, hydroxy esters **22a**,**b** were isolated with >99 and 94% de when derived from isomannide based compounds **17** and **18**, while analogous hydroxy esters **19b**,**d** were obtained from α-keto ester **13** with 88 and 65% de, respectively. Since such a dramatic increase in stereoselectivity was not observed with product **22c** resulting from addition on methyl protected compound **18**, the presence of a π-stacking between the dicarbonyl moiety and the phenyl ring of protecting group was hypothesized. A calculation of the most favored conformation of compound **17** (SYBYL 6.3, minimum global energy 36.8 Kcal/mol) confirmed a perfect parallelism between the phenyl moieties of the keto-ester and of the protecting group, and revealed a distance between the two rings characteristic for π-stacking (3.25 Å)[22] (Scheme 6).

3. Conclusion

In summary, mono-protected compounds **3–5** and **9–11** derived from isosorbide **1** and isomannide **2** were established as attractive alternatives to the classical chiral auxiliaries used for the asymmetric synthesis of tertiary α-hydroxy acids. Thus, hydroxy acids **20** and **23** were obtained after saponification in 60–99% ee by the addition of organozinc reagents to α-keto esters **13**, **14**, **17** and **18**. However, when compared to the commonly used



Scheme 6.

auxiliaries, isosorbide and isomannide derived auxiliaries advantageously allow the selective synthesis of tertiary α-hydroxy acids in both enantiomeric forms, by an adapted choice of either the protecting group or of the starting diol.

4. Experimental

4.1. General methods

^1H, ^{13}C NMR spectra were recorded on a 250 MHz NMR spectrometer (250 and 62.5 MHz, respectively) using $CDCl_3$ as solvent and tetramethylsilane as internal standard. Solvents were distilled under argon immediately before use from sodium/benzophenone. All other reagents were obtained from commercial sources and were used without purification.

4.2. General procedure for the preparation of compounds 3–5

Compound **3** was synthesized according to a described procedure.[18] Compound **4** was obtained by adapting a known protocol[18] and performing the reaction at room temperature instead of 90°C. Both products were obtained by precipitation from cold diethyl ether. All spectral data were found identical to those reported[18] except the following.

4.2.1. (1*R*,4*S*,5*R*,8*R*)-4-Benzyloxy-2,6-dioxabicyclo[3.3.0]-octanol 3. White solid (40%), ^1H NMR δ 2.73 (d, J=7.1 Hz, 1H), 3.58 (dd, J=5.9, 9.7 Hz, 1H), 3.85 (dd, J=6.2, 9.7 Hz, 1H), 3.88 (dd, J=3.5, 10.3 Hz, 1H), 4.09 (d, J=10.3 Hz, 1H), 4.12 (d, J=3.5 Hz, 1H), 4.28 (dddd, J=5.1, 5.9, 6.2, 7.1 Hz, 1H), 4.53 (d, J=4.8 Hz, 1H), 4.58 (d, J=2.8 Hz, 2H), 4.64 (dd, J=4.8, 5.5 Hz, 1H), 7.30–7.40 (m, 5H).

4.2.2. (1*R*,4*S*,5*R*,8*R*)-8-Benzyloxy-2,6-dioxabicyclo[3.3.0]-octanol 4. White solid (60%), ^1H NMR δ 1.78 (d, J=5.0 Hz, 1H), 3.58 (dd, J=7.5, 8.8 Hz, 1H), 3.83 (dd, J=6.3, 8.8 Hz, 1H), 3.97–4.00 (m, 2H), 4.03 (ddd, J=6.3, 7.5, 7.6 Hz, 1H), 4.31 (bs, 1H), 4.40 (d, J=5.0 Hz, 1H), 4.55 (d, J=11.2 Hz, 1H), 4.70 (dd, J=5.0, 7.5 Hz, 1H), 4.75 (d, J=11.2 Hz, 1H), 7.30–7.40 (m, 5H).

4.2.3. (1*R*,4*R*,5*R*,8*R*)-4-Benzyloxy-2,6-dioxabicyclo[3.3.0]-octanol 5. Isomannide **2** (1 g, 6.85 mmol), potassium hydroxide (0.44 g, 6.85 mmol) were dissolved in H_2O (3.5 mL) and the resulting solution was heated to reflux for 20 min. The mixture was cooled to rt, benzyl chloride was added dropwise (0.78 mL, 6.85 mmol). The solution was refluxed for additional 3 h before an acidic quench (HCl 2N, 3.5 mL) and extraction with ethyl acetate (3× 2 mL). The combined organic layers were dried ($MgSO_4$) and concentrated under vacuum. The crude product was then precipitated in cold Et_2O (5 mL) to give **5** (0.73 g, 45%) as a white solid. Mp=93°C, ^1H NMR δ 2.85 (d, J= 8.5 Hz, 1H), 3.74–3.80 (m, 2H), 4.02–4.05 (m, 2H), 4.08 (dd, J=4.8, 8.1 Hz, 1H), 4.29 (dq, J=5.5, 8.5 Hz, 1H), 4.50 (dd, J=4.6, 5.5 Hz, 1H), 4.57 (dd, J=4.6, 4.8 Hz, 1H), 4.58 (d, J=11.8 Hz, 1H), 4.78 (d, J=11.8 Hz, 1H), 7.30–7.40 (m, 5H); ^{13}C NMR δ 71.4, 72.3, 72.6, 74.9, 78.9, 80.6, 81.7, 128.0, 131.0; IR (ν_{max}, cm^{-1}, film) 1220, 2850–3000, 3400; $[\alpha]_D^{20}$=+138° (c 1, $CHCl_3$); Anal. Calcd for $C_{13}H_{16}O_4$: C, 66.09; H, 6.83. Found: C, 65.69; H, 6.76.

4.3. General procedure for the preparation of compounds 6–8

Compounds **3**, **4** or **5** (2 g, 8.47 mmol), potassium hydroxide (0.66 g, 10.2 mmol) and Aliquat 336 (0.34 g, 0.85 mmol) were mixed and shaken for 20 min at rt. Methyl iodide (0.63 mL, 10.2 mmol) was added and the resulting mixture was stirred for 5 h at 30°C. Dilution with Et_2O (50 mL) followed by filtration over a pad of Celite, and concentration under vacuum gave a crude product which afforded compounds **6**, **7** or **8** (2.11 g, quant) as yellow oils, upon flash column chromatography on silica gel (pentane/ethyl acetate: 50/50).

4.3.1. (1*R*,4*S*,5*R*,8*R*)-4-Benzyloxy-8-methoxy-2,6-dioxabicyclo-[3.3.0]octanol. 6: (≥98%) spectral data were found identical to those published.[18]

4.3.2. (1*R*,4*S*,5*R*,8*R*)-8-Benzyloxy-4-methoxy-2,6-dioxabicyclo[3.3.0]octanol 7. (≥98%), ^1H NMR δ 3.38 (s, 3H), 3.62 (dd, J=7.0, 8.4 Hz, 1H), 3.82–3.85 (m, 2H), 3.95–4.00 (m, 2H), 4.03 (dt, J=5.6, 7.0 Hz, 1H), 4.49 (d, J=4.2 Hz, 1H), 4.55 (d, J=11.2 Hz, 2H), 4.65 (dd, J=5.6, 4.2 Hz, 1H), 4.77 (d, J=11.2 Hz, 2H), 7.30–7.40 (m, 5H); ^{13}C NMR δ 56.9, 69.2, 72.1, 72.8, 78.9, 80.0, 85.6, 85.7, 128.0, 137.6; IR (ν_{max}, cm^{-1}, film) 1100, 1210, 1360, 1450, 2850–3000; $[\alpha]_D^{20}$=+114° (c 1.35, $CHCl_3$); Anal. Calcd for $C_{14}H_{18}O_4$: C, 67.18; H, 7.25. Found: C, 67.40; H, 7.24.

4.3.3. (1*R*,4*R*,5*R*,8*R*)-8-Benzyloxy-4-methoxy-2,6-dioxabicyclo[3.3.0]octanol 8. (≥98%), ^1H NMR δ 3.45 (s, 3H), 3.72–3.80 (m, 2H), 3.87–4.12 (m, 4H), 4.53–4.54 (m, 2H), 4.55 (d, J=12.3 Hz, 2H), 4.73 (d, J=12.3 Hz, 2H), 7.30–7.40 (m, 5H); ^{13}C NMR δ 58.1, 70.7, 70.9, 72.2, 79.1, 79.9, 80.3, 81.7, 128.0, 137.5; IR (ν_{max}, cm^{-1}, film) 1080, 1100, 1150, 1220, 1370, 1380, 1450, 2850–3000; $[\alpha]_D^{20}$=+160° (c 1.11, $CHCl_3$); Anal. Calcd for $C_{14}H_{18}O_4$: C, 67.18; H, 7.25. Found: C, 67.55; H, 7.26.

4.4. General procedure for the preparation of compounds 9–11

Pd/C (~30 mg) was added to a solution of **6**, **7** or **8** (0.2 g, 0.85 mmol) in absolute ethanol (15 mL) and the mixture was stirred for 2 h under hydrogen atmosphere. After filtration of the suspension over a pad of Celite followed by extensive washes (ethanol), the combined layers were concentrated to afford pure compounds **9**, **10** or **11** (126 mg, quant).

4.4.1. (1*R*,4*S*,5*R*,8*R*)-8-Methoxy-2,6-dioxabicyclo[3.3.0]-octanol 9. Colorless oil (≥98%), spectral data were found identical to those published.[18]

4.4.2. (1*R*,4*S*,5*R*,8*R*)-4-Methoxy-2,6-dioxabicyclo[3.3.0]-octanol 10. Colorless oil (≥98%), ^1H NMR δ 2.85 (bs, 1H), 3.40 (s, 3H), 3.57 (dd, J=6.2, 9.4 Hz, 1H), 3.90 (m, 3H), 4.06 (d, J=9.6 Hz, 1H), 4.27 (dt, J=5.0, 6.2 Hz, 1H), 4.47 (d, J=4.5 Hz, 1H), 4.60 (dd, J=4.5, 5.0 Hz, 1H); all other spectral data were found identical to those reported.[14]

4.4.3. (1*R*,4*R*,5*R*,8*R*)-4-Methoxy-2,6-dioxabicyclo[3.3.0]-octanol 11. Colorless solid (≥98%); mp=72°C; ^{1}H NMR δ 2.46 (d, *J*=8.7 Hz, 1H), 3.49 (s, 3H), 3.65–3.77 (m, 2H), 3.90–4.15 (m, 3H), 4.29 (qd, *J*=5.8, 8.7 Hz, 1H), 4.53 (dd, *J*= 4.9, 5.8 Hz, 1H), 4.57 (dd, *J*=4.4, 4.9 Hz, 1H); ^{13}C NMR δ 58.4, 71.0, 72.3, 74.9, 80.2, 81.5, 81.9; IR (ν_{max}, cm^{-1}, film) 1400, 1450, 2850–3000, 3450; $[\alpha]_D^{20}$=+113° (*c* 1.41, $CHCl_3$); Anal. Calcd for $C_7H_{12}O_4$: C, 52.49; H, 7.55. Found: C, 52.78; H, 7.31.

4.5. General procedure for the preparation of compounds 12–18

According to the nature of the ketoester prepared, either glyoxylic or pyruvic acids (1.5 equiv.) and *para*-toluenesulfonic acid (3% mol) were added to solutions of compound **3**–**5** or **11** in toluene (0.15 M). A Dean–Stark apparatus was adapted and the mixture was refluxed for 24 h. The solution was washed with saturated aqueous $NaHCO_3$ and then with H_2O until neutral pH was obtained. After drying ($MgSO_4$), the organic layer was concentrated under vacuum to afford a crude product which was purified by flash column chromatography on silica gel (pentane/ethyl acetate: 50/50).

4.5.1. [8-(1*R*,4*S*,5*R*,8*R*)-4-Benzyloxy-2,6-dioxabicyclo-[3.3.0]octane]-(2-oxo)-propanoate 12. Yellow oil (quant); ^{1}H NMR δ 2.50 (s, 3H), 3.86 (dd, *J*=4.4, 10.4 Hz, 1H), 3.90–4.13 (m, 4H), 4.55 (d, *J*=4.5 Hz, 1H), 4.59 (s, 2H), 4.82 (dd, *J*=4.5, 5.9 Hz, 1H), 5.25 (ddd, *J*=5.6, 5.8, 6.1 Hz, 1H), 7.35 (m, 5H); ^{13}C NMR δ 26.6, 70.5, 72.3, 73.4, 78.8, 80.3, 82.0, 85.5, 128.0, 137.5, 160.0, 191.0; IR (ν_{max}, cm^{-1}, film) 1220, 1430, 1530, 1740, 2850–3000; Anal. Calcd for $C_{16}H_{18}O_6$: C, 62.74; H, 5.92. Found: C, 62.41; H, 5.87.

4.5.2. [8-(1*R*,4*S*,5*R*,8*R*)-4-Benzyloxy-2,6-dioxabicyclo-[3.3.0]octane]-(2-oxo-2-phenyl)-ethanoate 13. Sticky beige oil (95%); ^{1}H NMR δ 3.79 (dd, *J*=3.5, 10.1 Hz, 1H), 3.95 (dd, *J*=5.3, 10.1 Hz, 1H), 4.10–4.13 (m, 3H), 4.57 (d, *J*=5.3 Hz, 1H), 4.58 (s, 2H), 5.06 (dd, *J*=5.3, 5.4 Hz, 1H), 5.40 (ddd, *J*=5.3, 5.4, 5.7 Hz, 1H), 7.35–7.40 (m, 5H), 7.52 (dd, *J*=7.2, 7.9 Hz, 1H), 7.69 (dd, *J*=7.4, 7.9 Hz, 1H), 8.11 (d, *J*=7.2 Hz, 2H); ^{13}C NMR δ 70.3, 71.1, 72.8, 75.7, 80.4, 82.5, 86.2, 130.0, 133.3, 137.2, 163.0, 186.0; IR (ν_{max}, cm^{-1}, film) 1450, 1600, 1680, 1750, 2850–3000; $[\alpha]_D^{20}$=+76° (*c* 1, $CHCl_3$); Anal. Calcd for $C_{21}H_{20}O_6$: C, 68.47; H, 5.47. Found: C, 68.22; H, 5.75.

4.5.3. [8-(1*R*,4*S*,5*R*,8*R*)-4-Methoxy-2,6-dioxabicyclo[3.3.0]-octane]-(2-oxo-2-phenyl)-ethanoate 14. Beige solid recrystallized from hexanes (65%); mp=80°C; ^{1}H NMR δ 3.39 (s, 3H), 3.76 (dd, *J*=3.5, 10.9 Hz, 1H), 3.85–4.07 (m, 4H), 4.51 (d, *J*=6.2 Hz, 1H), 5.01 (t, *J*=6.2 Hz, 1H), 5.40 (ddd, *J*=5.9, 6.0, 6.2 Hz, 1H), 7.52 (dd, *J*=7.8, 7.9 Hz, 2H), 7.69 (dd, *J*=6.2, 7.8 Hz, 1H), 8.12 (d, *J*=6.2 Hz, 2H); ^{13}C NMR δ 57.0, 70.5, 72.6, 75.6, 80.5, 84.9, 85.9, 129.0, 135.0, 163.0, 186.0; IR (ν_{max}, cm^{-1}, film) 1100, 1200, 1350, 1450, 1680, 1725, 2850–2950; $[\alpha]_D^{20}$=+79° (*c* 1.23, $CHCl_3$); Anal. Calcd for $C_{15}H_{16}O_6$: C, 61.64; H, 5.52. Found: C, 61.28; H, 5.41.

4.5.4. [4-(1*R*,4*S*,5*R*,8*R*)-8-Benzyloxy-2,6-dioxabicyclo-[3.3.0]octane]-(2-oxo-2-phenyl)-ethanoate 15. Orange oil (87%); ^{1}H NMR δ 3.70 (dd, *J*=6.9, 10.4 Hz, 1H), 3.89 (dd, *J*=6.9, 10.4 Hz, 1H), 4.00–4.05 (m, 2H), 4.08 (dt, *J*=6.8, 6.9 Hz, 1H), 4.55 (d, *J*=12.1 Hz, 1H), 4.61 (d, *J*=5.2 Hz, 1H), 4.72 (dd, *J*=5.2, 6.9 Hz, 1H), 4.78 (d, *J*=12.1 Hz, 1H), 5.45 (dd, *J*=3.2, 3.5 Hz, 1H), 7.30–7.40 (m, 5H), 7.51 (dd, *J*=6.9, 8.6 Hz, 2H), 7.68 (dd, *J*=6.9, 8.6 Hz, 1H), 7.98 (d, *J*=6.9 Hz, 2H); ^{13}C NMR δ 70.6, 72.5, 73.3, 78.8, 80.1, 80.7, 85.6, 128.4, 135.1, 137.5, 162.8, 185.3; IR (ν_{max}, cm^{-1}, film) 1180, 1450, 1600, 1690, 1740, 2850–3000; $[\alpha]_D^{20}$=+81° (*c* 1.64, $CHCl_3$); Anal. Calcd for $C_{21}H_{20}O_6$: C, 68.47; H, 5.47. Found: C, 68.07; H, 5.74.

4.5.5. [4-(1*R*,4*S*,5*R*,8*R*)-8-Benzyloxy-2,6-dioxabicyclo-[3.3.0]octane]-(2-oxo)-propanoate 16. Orange oil (70%); ^{1}H NMR δ 2.48 (s, 3H), 3.69 (dd, *J*=5.9, 8.9 Hz, 1H), 3.89 (dd, *J*=7.4, 8.9 Hz, 1H), 4.02–4.13 (m, 3H), 4.56 (d, *J*=11.9 Hz, 1H), 4.60 (d, *J*=2.9 Hz, 1H), 4.77 (dd, *J*=2.9, 5.9 Hz, 1H), 4.80 (d, *J*=11.9 Hz, 1H), 5.26 (dd, *J*=2.9, 3.1 Hz, 1H), 7.30–7.40 (m, 5H); ^{13}C NMR δ 26.6, 70.5, 72.3, 73.4, 78.8, 80.3, 82.0, 85.5, 128.0, 137.5, 160.0, 191.0; IR (ν_{max}, cm^{-1}, film) 1210, 1410, 1510, 1730, 2850–3000; $[\alpha]_D^{20}$=+100° (*c* 0.98, $CHCl_3$); Anal. Calcd for $C_{16}H_{18}O_6$: C, 62.74; H, 5.92. Found: C, 62.44; H, 5.81.

4.5.6. 4-(1*R*,4*R*,5*R*,8*R*)-8-Benzyloxy-2,6-dioxabicyclo-[3.3.0]octane]-(2-oxo-2-phenyl)-ethanoate 17. Yellow oil (55%); ^{1}H NMR δ 3.60 (dd, *J*=8.7, 8.8 Hz, 1H), 3.92 (dd, *J*=6.9, 8.8 Hz, 1H), 4.00–4.20 (m, 3H), 4.54 (dd, *J*=3.2, 4.9 Hz, 1H), 4.58 (d, *J*=11.8 Hz, 1H), 4.73 (d, *J*=11.8 Hz, 1H), 4.90 (dd, *J*=4.9, 5.9 Hz, 1H), 5.35 (ddd, *J*=4.9, 5.6, 5.9 Hz, 1H), 7.30–7.40 (m, 5H), 7.49 (dd, *J*=7.4, 7.8 Hz, 2H), 7.65 (dd, *J*=7.1, 7.5 Hz, 1H), 8.08 (d, *J*=7.2 Hz, 2H); ^{13}C NMR δ 70.2, 71.0, 72.4, 75.9, 78.4, 80.3, 80.4, 128.0, 134.9, 137.4, 163.3, 186.0; IR (ν_{max}, cm^{-1}, film) 1200, 1450, 1600, 1680, 1740, 2850–3000; $[\alpha]_D^{20}$=+174° (*c* 1.12, $CHCl_3$); Anal. Calcd for $C_{21}H_{20}O_6$: C, 68.47; H, 5.47. Found: C, 68.85; H, 5.37.

4.5.7. 8-(1*R*,4*R*,5*R*,8*R*)-4-Methoxy-2,6-dioxabicyclo-[3.3.0]octane]-(2-oxo-2-phenyl)-ethanoate 18. Yellow oil (68%); ^{1}H NMR δ 3.41 (s, 3H), 3.51 (dd, *J*=7.5, 8.9 Hz, 1H), 3.83–4.11 (m, 4H), 4.52 (dd, *J*=4.4, 5.9 Hz, 1H), 4.90 (t, *J*=5.9 Hz, 1H), 5.31 (dt, *J*=5.9, 6.1 Hz, 1H), 7.47 (dd, *J*=5.9, 7.4 Hz, 2H), 7.62 (dd, *J*=5.9, 7.4 Hz, 1H), 8.02 (d, *J*=5.9 Hz, 2H); ^{13}C NMR δ 57.8, 70.0, 71.0, 76.0, 79.5, 80.5, 81.0, 128.0, 135.0, 163.0, 185.9; IR (ν_{max}, cm^{-1}, film) 1300, 1450, 1600, 1685, 1740, 2850–2950; $[\alpha]_D^{20}$=+137° (*c* 1.25, $CHCl_3$); Anal. Calcd for $C_{15}H_{16}O_6$: C, 61.64; H, 5.52. Found: C, 61.31; H, 5.53.

4.6. General procedure for the preparation of compounds 19, 21, 22

A solution of $ZnCl_2$ in Et_2O (1 M, 1 mmol) was added to ketoesters **13**, **15**, **17** or **18** (0.5 mmol) in THF (5 mL). In a separated flask, a solution of Grignard reagent (2 mmol) was added drop by drop to a solution of $ZnCl_2$ (2 mmol). Both flasks were then gently shaken for 1 h at rt. The solution of the prepared organozinc reagent was then slowly added to the solution of the pre-complexed ketoester pre-cooled to the temperature of choice. After complete conversion of the starting material (TLC monitoring), saturated aqueous NH_4Cl (4 mL) is added and the mixture is warmed up to rt. Extraction of the solution with Et_2O (2×5 mL), followed

by drying and concentration of the combined organic layers afford crude compound **19**, **21** or **22**, which are purified by flash column chromatography on silica gel (pentane/ethyl acetate gradients).

4.6.1. [8-(1*R*,4*S*,5*R*,8*R*)-4-Benzyloxy-2,6-dioxabicyclo-[3.3.0]octane]-(2-hydroxy-2-phenyl)-butanoate 19a. Colorless oil (65%); ^{1}H NMR δ 0.90 (dd, J=6.6, 7.9 Hz, 3H), 2.19–2.21 (m, 2H), 3.20 (dd, J=3.9, 10.5 Hz, 1H), 3.61 (d, J=10.5 Hz, 1H), 3.80–3.97 (m, 3H), 4.41 (d, J=5.3 Hz, 1H), 4.50 (s, 2H), 4.80 (dd, J=5.3, 5.4 Hz, 1H), 4.83–4.87 (m, 1H), 5.13 (q, J=5.4 Hz, 1H), 7.32–7.38 (m, 8H), 7.61 (d, J=5.3 Hz, 2H); ^{13}C NMR δ 7.9, 32.2, 70.6, 71.1, 72.2, 75.6, 78.5, 80.6, 82.5, 86.2, 127.0, 137.4, 141.3, 174.6; IR (ν_{max}, cm^{-1}, film) 1220, 1430, 1500, 1730, 2850–3000, 3600; $[\alpha]_D^{20}$=+49° (c 0.98, $CHCl_3$); Anal. Calcd for $C_{23}H_{26}O_6$: C, 69.33; H, 6.58. Found: C, 68.94; H, 6.61.

4.6.2. [8-(1*R*,4*S*,5*R*,8*R*)-4-Benzyloxy-2,6-dioxabicyclo-[3.3.0]octane]-(2-hydroxy-3-methyl-2-phenyl)-butanoate 19b. Yellow oil (78%); ^{1}H NMR δ 0.75 (d, J=6.2 Hz, 3H), 1.00 (d, J=6.2 Hz, 3H), 2.65 (d, J=6.2 Hz, 1H), 3.25 (dd, J=3.7, 10.0 Hz, 1H), 3.65 (d, J=10.0 Hz, 1H), 3.82–4.00 (m, 3H), 4.41 (d, J=5.0 Hz, 1H), 4.48 (s, 2H), 4.75 (dd, J=5.0, 6.2 Hz, 1H), 4.82–4.87 (m, 1H), 5.08 (q, J=6.2 Hz, 1H), 7.33–7.36 (m, 8H), 7.67 (d, J=7.5 Hz, 2H); ^{13}C NMR δ 15.7, 17.0, 35.2, 70.5, 71.0, 72.2, 75.8, 80.5, 80.7, 82.5, 86.2, 128.0, 137.4, 140.7, 174.9; IR (ν_{max}, cm^{-1}, film) 1220, 1420, 1520, 1720, 2850–3000, 3600; $[\alpha]_D^{20}$=+39° (c 0.98, $CHCl_3$); Anal. Calcd for $C_{24}H_{28}O_6$: C, 69.89; H, 6.84. Found: C, 69.67; H, 6.84.

4.6.3. [8-(1*R*,4*S*,5*R*,8*R*)-4-Benzyloxy-2,6-dioxabicyclo-[3.3.0]octane]-(2-hydroxy-2-phenyl)-hexanoate 19c. Yellow oil (75%); ^{1}H NMR δ 0.90 (dd, J=5.9, 7.1 Hz, 3H), 1.22–1.42 (m, 4H), 1.95–2.30 (m, 2H), 3.20 (dd, J=3.6, 10.7 Hz, 1H), 3.61 (d, J=10.7 Hz, 1H), 3.80–4.00 (m, 3H), 4.41 (d, J=4.8 Hz, 1H), 4.50 (s, 2H), 4.79 (dd, J=4.8, 5.9 Hz, 1H), 4.83–4.87 (m, 1H), 5.11 (q, J=5.9 Hz, 1H), 7.32–7.38 (m, 8H), 7.60 (d, J=7.1 Hz, 2H); ^{13}C NMR δ 13.9, 22.6, 25.5, 38.9, 70.6, 71.0, 72.2, 75.5, 78.1, 80.6, 82.5, 86.2, 128.0, 137.4, 141.5, 174.6; IR (ν_{max}, cm^{-1}, film) 1200, 1710, 2850–3000, 3550; $[\alpha]_D^{20}$=+19° (c 1.08, $CHCl_3$); Anal. Calcd for $C_{25}H_{30}O_6$: C, 70.40; H, 7.09. Found: C, 70.46; H, 7.23.

4.6.4. [8-(1*R*,4*S*,5*R*,8*R*)-4-Benzyloxy-2,6-dioxabicyclo-[3.3.0]octane]-(2-hydroxy-4-methyl-2-phenyl)-pentanoate 19d. Colorless oil (48%); ^{1}H NMR δ 0.90 (d, J=7.1 Hz, 6H), 1.82–1.86 (m, 1H), 2.11–2.14 (m, 2H), 3.23 (dd, J=3.6, 9.5 Hz, 1H), 3.61 (d, J=9.5 Hz, 1H), 3.80–4.00 (m, 3H), 4.42 (d, J=4.8 Hz, 1H), 4.50 (s, 2H), 4.80 (dd, J=4.8, 5.9 Hz, 1H), 4.83–4.87 (m, 1H), 5.10 (q, J=5.9 Hz, 1H), 7.32–7.38 (m, 8H), 7.64 (d, J=7.1 Hz, 2H); ^{13}C NMR δ 23.3, 24.3, 34.0, 47.3, 70.5, 71.1, 72.4, 76.5, 78.6, 80.6, 82.6, 86.2, 128.0, 137.4, 142.3, 175.0; IR (ν_{max}, cm^{-1}, film) 1100, 1200, 1720, 2850–3000, 3500; $[\alpha]_D^{20}$=+35° (c 0.87, $CHCl_3$); Anal. Calcd for $C_{25}H_{30}O_6$: C, 70.40; H, 7.09. Found: C, 70.36; H, 7.16.

4.6.5. [8-(1*R*,4*S*,5*R*,8*R*)-4-Benzyloxy-2,6-dioxabicyclo-[3.3.0]octane]-(3,3-dimethyl-2-hydroxy-2-phenyl)-butanoate 19e. Light yellow oil (27%); ^{1}H NMR δ 1.05 (s, 9H), 3.68–4.18 (m, 5H), 4.52–4.57 (m, 3H), 4.86 (dd, J=4.5, 5.9 Hz, 1H), 4.98–5.09 (m, 1H), 5.12 (q, J=5.9 Hz, 1H), 7.27–7.33 (m, 8H), 7.68–7.73 (m, 2H); ^{13}C NMR δ 25.6, 69.8, 71.4, 72.9, 75.6, 78.2, 80.4, 82.9, 86.3, 128.0, 136.0, 138.0, 174.0; IR (ν_{max}, cm^{-1}, film) 1100, 1250, 1720, 2850–3000, 3400; $[\alpha]_D^{20}$=+36° (c 0.55, $CHCl_3$); Anal. Calcd for $C_{25}H_{30}O_6$: C, 70.40; H, 7.09. Found: C, 70.48; H, 7.13.

4.6.6. [8-(1*R*,4*S*,5*R*,8*R*)-4-Benzyloxy-2,6-dioxabicyclo-[3.3.0]octane]-(2-hydroxy-2-phenyl)-pent-4-enoate 19f. Yellow oil (50%); ^{1}H NMR δ 2.80 (dd, J=7.5, 14.9 Hz, 1H), 3.02 (dd, J=7.5, 14.9 Hz, 1H), 3.25 (dd, J=4.5, 10.4 Hz, 1H), 3.60–4.05 (m, 4H), 4.47–4.52 (m, 3H), 4.78 (dd, J=4.5, 5.9 Hz, 1H), 4.83–4.86 (m, 1H), 5.06–5.26 (m, 3H), 5.82 (ddt, J=7.1, 7.4, 7.6 Hz, 1H), 7.33–7.38 (m, 8H), 7.60 (d, J=7.5 Hz, 2H); ^{13}C NMR δ 44.2, 70.4, 71.2, 72.4, 75.6, 80.5, 80.6, 82.8, 86.3, 119.5, 128.0, 132.3, 137.4, 140.8, 173.8; IR (ν_{max}, cm^{-1}, film) 1200, 1420, 1500, 1720, 2850–3000, 3600; $[\alpha]_D^{20}$=+44° (c 0.79, $CHCl_3$); Anal. Calcd for $C_{24}H_{26}O_6$: C, 70.23; H, 6.38. Found: C, 70.12; H, 6.41.

4.6.7. [8-(1*R*,4*S*,5*R*,8*R*)-4-Benzyloxy-2,6-dioxabicyclo-[3.3.0]octane]-(2-cyclohexyl-2-hydroxy-2-phenyl)-ethanoate 19g. Yellow oil (62%); ^{1}H NMR δ 1.02–1.85 (m, 10H), 2.22–2.27 (m, 1H), 3.23 (dd, J=3.0, 9.5 Hz, 1H), 3.61–3.65 (m, 2H), 3.82–3.95 (m, 2H), 4.40 (d, J=4.5 Hz, 1H), 4.50 (s, 2H), 4.75 (dd, J=4.5, 5.9 Hz, 1H), 4.83–4.86 (m, 1H), 5.05–5.16 (m, 1H), 7.30–7.35 (m, 8H), 7.60 (d, J=7.5 Hz, 2H); ^{13}C NMR δ 25.5, 27.2, 45.3, 70.7, 71.2, 72.3, 75.8, 80.6, 80.9, 82.7, 86.4, 128.0, 137.0, 140.4, 174.9; IR (ν_{max}, cm^{-1}, film) 1200, 1730, 2850–3000, 3600; $[\alpha]_D^{20}$=+39° (c 0.78, $CHCl_3$); Anal. Calcd for $C_{27}H_{32}O_6$: C, 71.66; H, 7.13. Found: C, 71.54; H, 7.34.

4.6.8. [8-(1*R*,4*S*,5*R*,8*R*)-4-Benzyloxy-2,6-dioxabicyclo-[3.3.0]octane]-(2-hydroxy-2,3-diphenyl)-propanoate 19h. Colorless oil (58%); ^{1}H NMR δ 3.25 (d, J=14.3 Hz, 1H), 3.30 (dd, J=3.6, 9.5 Hz, 1H), 3.61 (d, J=14.3 Hz, 1H), 3.68 (d, J=9.5 Hz, 1H), 3.82–4.00 (m, 3H), 4.42 (d, J=4.8 Hz, 1H), 4.50 (s, 2H), 4.75 (dd, J=4.8, 5.9 Hz, 1H), 4.82–4.87 (m, 1H), 5.00 (q, J=5.9 Hz, 1H), 7.18–7.40 (m, 13H), 7.70 (d, J=7.1 Hz, 2H); ^{13}C NMR δ 45.4, 70.3, 71.2, 72.5, 75.8, 78.6, 80.7, 82.7, 86.2, 128.0, 135.6, 137.4, 141.3, 173.8; IR (ν_{max}, cm^{-1}, film) 1200, 1420, 1500, 1720, 2850–3000, 3500; $[\alpha]_D^{20}$=+7° (c 1, $CHCl_3$); Anal. Calcd for $C_{28}H_{28}O_6$: C, 73.03; H, 6.13. Found: C, 73.39; H, 6.51.

4.6.9. [4-(1*R*,4*S*,5*R*,8*R*)-8-Benzyloxy-2,6-dioxabicyclo-[3.3.0]octane]-(2-hydroxy-2-phenyl)-butanoate 21a. Yellow oil (48%); ^{1}H NMR δ 0.92 (dd, J=5.9, 7.1 Hz, 3H), 1.92–2.30 (m, 2H), 3.55–4.20 (m, 5H), 4.50 (d, J=4.8 Hz, 1H), 4.55 (d, J=11.9 Hz, 1H), 4.70 (dd, J=4.8, 5.9 Hz, 1H), 4.77 (d, J=11.9 Hz, 1H), 5.25 (d, J=3.6 Hz, 1H), 7.30–7.45 (m, 8H), 7.57 (d, J=7.0 Hz, 2H); ^{13}C NMR δ 8.0, 32.5, 60.0, 70.5, 72.5, 73.1, 78.7, 80.0, 80.6, 85.4, 128.0, 137.5, 141.3, 174.2; IR (ν_{max}, cm^{-1}, film) 1200, 1400, 1500, 1715, 2850–3000, 3500; $[\alpha]_D^{20}$=+89° (c 1.39, $CHCl_3$); Anal. Calcd for $C_{23}H_{26}O_6$: C, 69.33; H, 6.58. Found: C, 68.95; H, 6.66.

4.6.10. [4-(1*R*,4*S*,5*R*,8*R*)-8-Benzyloxy-2,6-dioxabicyclo-[3.3.0]octane]-(2-hydroxy-3-methyl-2-phenyl)-butanoate 21b. Light yellow oil (51%); ^{1}H NMR δ 0.80 (d, J=7.0 Hz,

3H), 1.02 (d, J=7.0 Hz, 3H), 2.60 (h, J=7.0 Hz, 1H), 3.55–4.18 (m, 5H), 4.50–4.65 (m, 2H), 4.70 (dd, J=4.8, 5.9 Hz, 1H), 4.77 (d, J=11.9 Hz, 1H), 5.20 (d, J=3.6 Hz, 1H), 7.28–7.41 (m, 8H), 7.61 (d, J=8.0 Hz, 2H); ^{13}C NMR δ 15.7, 17.1, 35.6, 60.0, 70.6, 72.5, 73.1, 79.0, 80.1, 80.7, 85.3, 128.0, 137.6, 140.7, 174.7; IR (ν_{max}, cm^{-1}, film) 1200, 1450, 1510, 1725, 2850–3000, 3500; $[\alpha]_D^{20}$=+68° (c 2.24, $CHCl_3$); Anal. Calcd for $C_{24}H_{28}O_6$: C, 69.89; H, 6.84. Found: C, 69.54; H, 6.96.

4.6.11. [4-(1*R*,4*S*,5*R*,8*R*)-8-Benzyloxy-2,6-dioxabicyclo-[3.3.0]octane]-(2-hydroxy-2-phenyl)-hexanoate 21c. Light yellow oil (65%); ^{1}H NMR δ 0.87–0.92 (m, 3H), 1.11–1.50 (m, 4H), 1.96–2.28 (m, 2H), 3.55–4.13 (m, 5H), 4.48 (d, J=4.8 Hz, 1H), 4.53 (d, J=10.7 Hz, 1H), 4.65 (dd, J=4.8, 5.9 Hz, 1H), 4.75 (d, J=10.7 Hz, 1H), 5.22 (d, J=3.5 Hz, 1H), 7.25–7.40 (m, 8H), 7.55 (d, J=7.1 Hz, 2H); ^{13}C NMR δ 14.0, 22.6, 25.6, 39.1, 60.3, 70.4, 72.4, 73.1, 78.8, 79.8, 80.6, 85.3, 128.0, 137.4, 141.4, 174.3; IR (ν_{max}, cm^{-1}, film) 1200, 1430, 1530, 173074, 2850–3000, 3500; $[\alpha]_D^{20}$=+74° (c 2.1, $CHCl_3$); Anal. Calcd for $C_{25}H_{30}O_6$: C, 70.40; H, 7.09. Found: C, 70.03; H, 7.15.

4.6.12. [4-(1*R*,4*S*,5*R*,8*R*)-8-Benzyloxy-2,6-dioxabicyclo-[3.3.0]octane]-(2-hydroxy-2-phenyl)-pent-4-enoate 21d. Colorless oil (25%); ^{1}H NMR δ 2.79–2.82 (m, 1H), 2.97–3.02 (m, 1H), 3.57–4.20 (m, 5H), 4.48 (d, J=4.5 Hz, 1H), 4.55 (d, J=11.9 Hz, 1H), 4.68 (dd, J=4.5, 5.9 Hz, 1H), 4.76 (d, J=11.9 Hz, 1H), 5.10–5.35 (m, 3H), 5.78–5.81 (m, 1H), 7.30–7.45 (m, 8H), 7.55 (d, J=7.4 Hz, 2H); ^{13}C NMR δ 43.9, 60.3, 70.4, 72.5, 73.1, 78.9, 80.0, 80.6, 85.3, 119.3, 128.0, 132.0, 137.5, 140.8, 173.6; $[\alpha]_D^{20}$=+63° (c 2.60, $CHCl_3$); Anal. Calcd for $C_{24}H_{26}O_6$: C, 70.23; H, 6.38. Found: C, 70.62; H, 6.71.

4.6.13. [4-(1*R*,4*R*,5*R*,8*R*)-8-Benzyloxy-2,6-dioxabicyclo-[3.3.0]octane]-(2-hydroxy-3-methyl-2-phenyl)-butanoate 22a. Yellow oil (53%); ^{1}H NMR δ 0.75 (d, J=7.1 Hz, 3H), 1.00 (d, J=7.1 Hz, 3H), 2.65–2.68 (m, 1H), 3.15 (dd, J=5.9, 9.5 Hz, 1H), 3.48 (dd, J=8.3, 9.5 Hz, 1H), 3.60–4.20 (m, 3H), 4.40 (dd, J=4.8, 5.9 Hz, 1H), 4.50 (d, J=11.9 Hz, 1H), 4.66 (dd, J=4.8, 5.9 Hz, 1H), 4.70 (d, J=11.9 Hz, 1H), 5.10 (q, J=5.9 Hz, 1H), 7.30–7.40 (m, 8H), 7.55 (d, J=7.1 Hz, 2H); ^{13}C NMR δ 15.7, 17.0, 35.2, 69.1, 71.4, 72.5, 75.9, 78.4, 79.2, 80.3, 80.5, 128.0, 137.4, 140.7, 175.1; IR (ν_{max}, cm^{-1}, film) 1250, 1730, 2850–3000, 3500; $[\alpha]_D^{20}$=+82° (c 1.01, $CHCl_3$); Anal. Calcd for $C_{24}H_{28}O_6$: C, 69.89; H, 6.84. Found: C, 69.57; H, 6.49.

4.6.14. [4-(1*R*,4*R*,5*R*,8*R*)-8-Benzyloxy-2,6-dioxabicyclo-[3.3.0]octane]-(2-hydroxy-4-methyl-2-phenyl)-pentanoate 22b. Yellow oil (23%); ^{1}H NMR δ 0.93 (d, J=7.4 Hz, 3H), 1.80–1.85 (m, 1H), 2.00–2.20 (m, 2H), 3.08 (dd, J=8.4, 8.9 Hz, 1H), 3.43 (dd, J=7.0, 8.9 Hz, 1H), 3.85–4.05 (m, 3H), 4.40 (dd, J=4.85, 5.9 Hz, 1H), 4.50 (d, J=11.9 Hz, 1H), 4.68 (dd, J=4.5, 5.9 Hz, 1H), 4.70 (d, J=11.9 Hz, 1H), 5.10 (q, J=5.9 Hz, 1H), 7.27–7.40 (m, 8H), 7.66 (d, J=7.0 Hz, 2H); ^{13}C NMR δ 23.2, 24.4, 34.0, 47.3, 69.7, 71.4, 72.6, 75.8, 78.1, 78.4, 80.3, 80.8, 128.0, 137.1, 142.2, 175.4; $[\alpha]_D^{20}$=+78° (c 1.00, $CHCl_3$); Anal. Calcd for $C_{25}H_{30}O_6$: C, 70.40; H, 7.09. Found: C, 70.16; H, 7.36.

4.6.15. [8-(1*R*,4*R*,5*R*,8*R*)-4-Methoxy-2,6-dioxabicyclo-[3.3.0]octane]-(2-hydroxy-3-methyl-2-phenyl)-butanoate 22c. Light yellow oil (70%); ^{1}H NMR δ 0.75 (d, J=6.0 Hz, 3H), 1.00 (d, J=6.0 Hz, 3H), 2.70 (h, J=6.0 Hz, 1H), 3.05 (dd, J=8.3, 9.5 Hz, 1H), 3.43 (s, 3H), 3.50–4.08 (m, 4H), 4.42 (dd, J=4.5, 5.2 Hz, 1H), 4.70 (dd, J=5.2, 5.9 Hz, 1H), 4.80 (dd, J=5.1, 5.9 Hz, 1H), 5.11 (q, J=5.6 Hz, 1H), 7.25–7.40 (m, 3H), 7.66 (d, J=7.1 Hz, 2H); ^{13}C NMR δ 15.7, 17.0, 35.0, 58.2, 69.3, 71.5, 75.9, 79.9, 80.2, 80.7, 80.8, 128.0, 140.6, 175.1; IR (ν_{max}, cm^{-1}, film) 1240, 1350, 1450, 1710, 2850–3000, 3430; $[\alpha]_D^{20}$=+80° (c 1.01, $CHCl_3$); Anal. Calcd for $C_{18}H_{24}O_6$: C, 64.27 H, 7.19. Found: C, 64.27; H, 7.21.

4.7. General procedure for the preparation of compounds 20 and 23

A solution of KOH (2.5 mmol) in H_2O (2 mL) was added to compounds **19** or **22** (0.5 mmol) in MeOH (2 mL). The resulting mixture was heated up to reflux until complete conversion of the starting material (TLC monitoring in pentane/AcOEt/MeOH:70/23/3+1%AcOH). After concentration of the mixture, H_2O (2 mL) was added and the aqueous layer was extracted with ethyl acetate (3×5 mL). Aqueous HCl (2N) was added until acidic pH was reached and the aqueous layer was further extracted with ethyl acetate (3×5 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated under vacuum to afford pure compound **20** or **23**. (the acido-basic washing sequence was repeated when compounds were isolated with unsatisfactory purity).

All analytical data corresponding to compounds **20a–d,f,g** and **23a–c** were found identical to those disclosed in the literature.[6,7a,23]

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4. Note: Alkylations of 2-substituted 1,3-dioxolan-4-ones[5] or additions to chiral ketooxazolines[6] have been proposed as

alternative routes for the synthesis of α-hydroxy acids but both methods suffer from strong limitations.

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