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Highly stereocontrolled alkylation of protected 'diacetone hexulose aldehydes'

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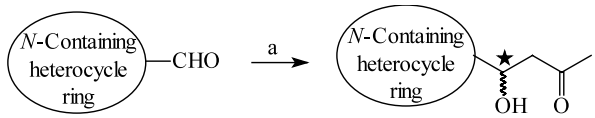
Abstract—Claisen–Schmidt aldol condensation (with acetone, catalysed by L- and D-proline), Knoevenagel reaction with acetoacetic acid and the modified Reformatsky reaction with bromoacetone of the 'diacetone hexulose aldehydes' **2** and **7** gave the corresponding β-hydroxyketones **3**–**4** and **8**–**9** as well as the (*E*)-α,β-enones **5** and **10**, respectively. The highest chemo- and stereoselectivities were obtained with the Knoevenagel procedure using L-proline as the catalyst.

1. Introduction

In connection with other works dealing with the stereoselective synthesis of bioactive compounds, and according to Scheme 1, we were interested in the transformation of the formyl group of complex protected polyhydroxylated piperidines and pyrrolidines (azasugars) into 1-hydroxy-3-oxobutyl appendage. With this aim, different synthetic strategies were envisaged where the Claisen–Schmidt and other related reactions (Knoevenagel, Reformatsky, etc.) could be used, but under the condition that the new stereogenic centre must be created in a highly stereocontrolled manner.

With the above objective in mind, the influence of the chirality, as well as the ring size, of the starting aldehyde on the stereochemical course of the process must be investigated, and thus two readily available 'diacetone hexulose aldehydes', namely 2,3:4,5-di-*O*-isopropylidene-β-D-*arabino*-hexos-2-ulopyranose[1] **2** and 2,3:4,6-di-*O*-isopropylidene-α-L-*xylo*-hexos-2-ulofuranose[2] **7**, were chosen as models.



Scheme 1. (a) Claisen–Schmidt, Knoevenagel, Reformatsky, etc.

The Claisen–Schmidt reaction between an aldehyde without α-hydrogens and a ketone under basic conditions, is a well-established procedure for the synthesis of β-hydroxyketones. When the reaction is conducted under the presence of an aldolase,[3] as a chiral basic catalyst, high stereoselectivity is observed. Recently[4] it has been reported that small basic chiral molecules, such as L- and D-proline, can act as 'mimics' of those enzymes giving high regio-, stereo- and enantioselectivities. Although this procedure has been applied to the simple acyclic carbohydrate derivative, 2,3-*O*-isopropylidene-D-glyceraldehyde,[4c] to the best of our knowledge, references about its use with more complex substrates, such as those for the above-mentioned **2** and **7**, have not been found in the literature, and in this context we report herein the results obtained from the application of this methodology to such compounds.

The Knoevenagel and Reformatsky reactions could lead to the already mentioned β-hydroxycarbonyl compounds and though both reactions have been previously applied in the carbohydrate field by our group,[5] and recently by others,[6] a comparative study of these reactions in the case of compounds **2** and **7** has been carried out and the results of this study are also detailed herein.

2. Results and discussion

The results of the Claisen–Schmidt condensation reaction between compounds **2** and **7** with acetone, catalysed by L-proline (see Scheme 2) are summarised in Table 1 (entries 1 and 2). In both cases the reaction proceeded with excellent stereoselectivity, thus the reac-

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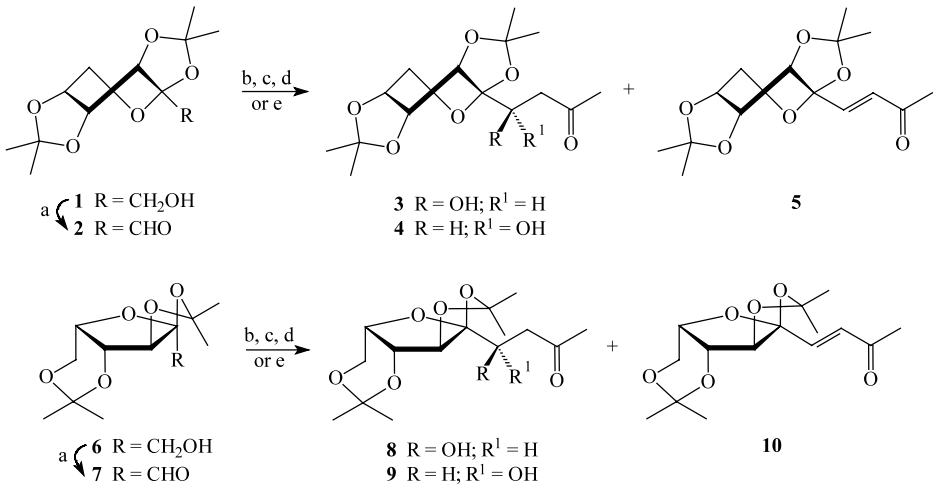


Scheme 2. (a) NMO/TPAP (cat.)/4 Å MS/Cl_2CH_2; (b) Me_2CO/DMSO/L-proline (cat.); (c) Me_2CO/DMSO/D-proline; (d) AAA/Et_2NH (cat.)/Et_2O–PhMe; (e) $BrCH_2COMe/Zn/I_2$ (cat.)/sonication.

tion of **2** afforded 1,3-dideoxy-5,6:7,8-di-*O*-isopropylidene-β-D-*manno*-non-2,5-diulo-5,9-pyranose **3** [(4*R*)-epimer, present in 99.1%], whereas **7** gave 1,3-dideoxy-5,6:7,9-di-*O*-isopropylidene-α-L-*gulo*-non-2,5-diulo-5,8-furanose **8** [(4*R*)-epimer, present in 93.1%]. In both cases, the (4*S*)-epimers were not detected at all. Under these conditions, the corresponding crotonization processes also proceeded in extremely low yield but with high stereoselectivity to afford the related (*E*)-α,β-enones: 1,3,4-trideoxy-5,6:7,8-di-*O*-isopropylidene-β-D-*arabino*-non-3-ene-2,5-diulo-5,9-pyranose **5** and 1,3,4-trideoxy-5,6:7,9-di-*O*-isopropylidene-α-L-*xylo*-non-3-ene-2,5-diulo-5,8-furanose **10**. When D-proline was used as the catalyst (entries 3 and 4) very low stereoselectivity was observed and compound **9** could not be isolated in pure form.

Table 1. Composition (%) of the reaction mixture from GLC analysis (A)

Compound	Time	(*R*)-Hk[a]	(*S*)-Hk[a]	α,β-Enone
2[b]	36 h	**3** (99.1)	–	**5** (0.9)
7[b]	4 days	**8** (93.1)	–	**10** (6.9)
2[c]	10 days	**3** (40.5)	**4** (55.1)	**5** (4.4)
7[c]	4 days	**8** (45.3)	**9** (33.9)	**10** (19.8)
2[d]	48 h	**3** (96.2)	**4** (2.3)	**5** (1.5)
7[d]	4 days	**8** (77.7)	**9** (11.4)	**10** (10.9)
2[e]	8 h	**3** (63.7)	–	**5** (36.3)
7[e]	2 h	**8** (57.9)	**9** (7.9)	**10** (34.2)

[a] β-Hydroxyketone.
[b] Catalysed by L-proline.
[c] Catalysed by D-proline.
[d] Knoevenagel reaction with AAA in PhMe/Et_2O catalysed by Et_2NH.
[e] Reformatsky reaction with bromopropanone/Zn catalysed by I_2.

Compounds **3**, **4**, **8** and **10** were characterised on the basis of their analytical and spectroscopic data (see Tables 2 and 3) and chemical correlation. Thus, the (4*R*)-configuration of **3** was determined by comparison of the chemical shifts of C(4) and C(6) with those seen for the same carbon atoms in **4** and application of the rule established by Costanzo et al.[6] who observed an upfield shift of 2 ppm in the major (*R*)-isomer with respect to the minor (*S*)-isomer in a series of analogous compounds.

GLC analysis (*C*) of the degradation products of **3** (**11**) and **8** (**12**) (see Scheme 3), allowed their identification by comparison of the respective R_t with those of authentic samples of methyl 2-deoxy-4,5:6,7-di-*O*-isopropylidene-β-D-*manno*-oct-4-ulo-4,8-pyranosonate **11** and methyl 2-deoxy-4,5:6,8-di-*O*-isopropylidene-α-L-*gulo*-oct-4-ulo-4,7-furanosonate **12** previously reported by our group.[5d]

Compound **5** showed the same physical and spectroscopic data previously reported.[7] Compound **10** was identified by comparison with an authentic sample prepared by Wittig reaction between **7** and 1-phosphoranylidene-2-propanone, where a minute amount of its (*Z*)-isomer was also present (GLC analysis, A).

The above stereochemical results can be justified (see Scheme 4) according to the literature,[4b,c] considering the free metal version of the chair-like Zimmerman–Traxler type transition states **A** and **B** and the boat-like **C**,[8] where the former (*ul*-topicity) is lacking in the 1,3-diaxial interaction between the bulky sugar-moiety and the methyl group of the L-proline enamine intermediate and hence is sterically less hindered and clearly favoured with respect to **B** or **C** (*lk*-topicity). In addition, the findings obtained with D-proline could be justified as a typical case of a catalyst–aldehyde chirality mismatched process.

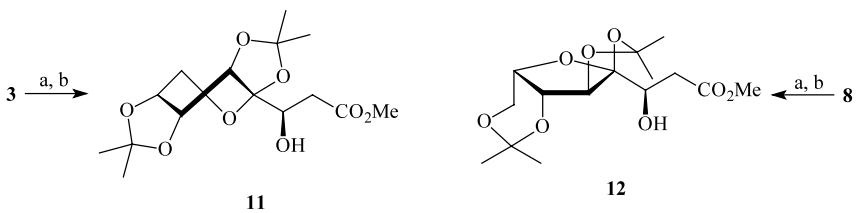
Table 2. ^{1}H NMR chemical shifts (δ) and J (Hz) values for compound **3**, **4**, **8** and **10**

Compound	H-1	H-3	H-3′	H-4	H-6	H-7	H-8	H-9	H-9′	CMe_2
3	2.20s	3.02dd $J_{3,4}$ 2.7 $J_{3,3'}$ 17.7	2.79dd $J_{3',4}$ 9.1	4.12dd	4.63–4.60m		4.23bd $J_{7,8}$ 7.7	3.91dd $J_{8,9}$ 1.7 $J_{9,9'}$ 13	3.74d	1.54 1.47 1.43 1.35
4	2.16s	2.81–2.79m		4.10dd $J_{3,4}$ 5.4 $J_{3',4}$ 6.8	4.35d $J_{6,7}$ 2.5	4.55dd $J_{7,8}$ 8	4.21bdd	3.48dd $J_{8,9}$ 2 $J_{9,9'}$ 13.1	3.75dd $J_{8,9'}$ 0.5	1.49 1.48 1.34 1.33
8	2.17s	2.99dd $J_{3,4}$ 2.9 $J_{3,3'}$ 17.5	2.79dd $J_{3',4}$ 9.2	4.24dd	4.53s	4.27d $J_{7,8}$ 2.1	4.07bt	4.04dd $J_{8,9}$ 2.2	3.96bd $J_{9,9'}$ 12.9	1.46 1.39 1.37 1.32
10	2.29s	6.28d $J_{3,4}$ 16	–	6.79d	4.33bs		4.12bt $J_{8,9}$ 1.6	4.07bd		1.51 1.42 1.35 1.34

Table 3. ^{13}C NMR chemical shifts (δ) for compound **3**, **4**, **8** and **10**

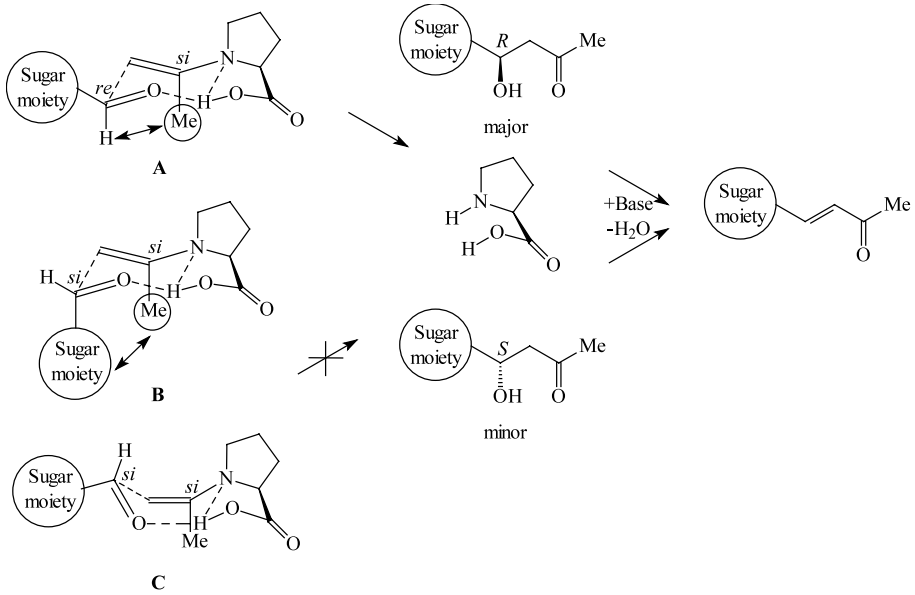
Compound	C-1	C-2	C-3	C-4	C-5	C-6	C-7	C-8	C-9	CMe_2	CMe_2
3	30.76	210.14	44.18	69.10	103.75	70.34	69.65	70.86	61.18	108.98 108.69	26.68 25.90 25.59 23.95
4	31.00	208.00	45.05	71.41	104.18	72.48	69.86	70.56	60.92	109.22 108.60	26.31 25.52 25.23 23.78
8	30.61	209.73	44.46	68.25	115.31	84.36	73.19	72.52	60.37	112.54 97.40	28.97 27.73 26.64 18.59
10	27.67	198.49	131.56	142.55	112.01	88.01	73.38[a]	73.10[a]	60.21	112.68 97.53	29.06 27.08 26.23 18.66

[a] Assigments may be interchanged.

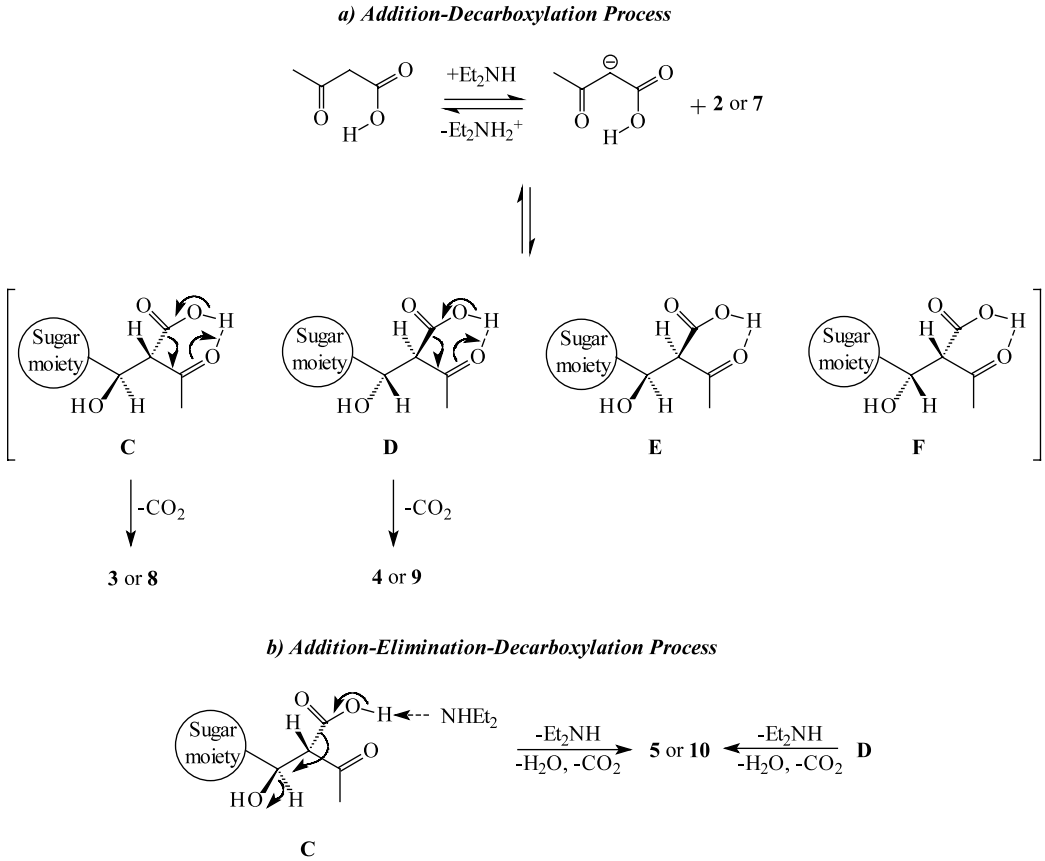


Scheme 3. (a) Aq. NaBrO; H_3O^+; (b) N_2CH_2/ether–methanol.

In the same way, the high chemo- and stereoselectivity found in the Knoevenagel reactions of **2** and **7** with acetoacetic acid merit mention (see Table 1, entries 5 and 6), these are similar to the best results obtained using L-proline as the catalyst. An explanation can be seen in Scheme 5, where all four possible intermediate adducts (**C**–**F**) are represented. According to the literature,[5c] depending on the reaction conditions, the adducts could form in two different ways. Under the actual conditions used in this work (non-basic solvent), the favoured decarboxylation reaction of **C** and **D** would afford (*R*)-**3** and the (*S*)-β-hydroxyketone **4** and by an elimination–decarboxylation reaction, the corresponding (*E*)-α,β-enone **5**, whereas adducts **E** and **F**



Scheme 4.



Scheme 5.

would produce the same β-hydroxyketones and the related (*Z*)-isomer, not observed in the reaction. The results shown in Table 1 are in accordance with the relative calculated[9] energies for the four possible adducts **C**–**F** (see Table 4) where **C** and **D** would be responsible for the formation of the main product **3** or **8** and to a lesser extent for that of **4** or **9** and **5** or **10**. The lower stability of intermediate adducts **E** and **F** accounts for the absence of the (*Z*)-α,β-enone.

The results from the Reformatsky reaction (see Table 1) between **2** and **7** and bromopropanone/Zn, in contrast to those with methyl bromoacetate[5d] were unsuccessful, since poor chemo- and stereoselectivity was obtained.

Table 4. Relative calculated energies (kcal/mol) respect to the most stable adduct **C**

Compound	Adducts			
	C	D	E	F
2	0	+0.99	+2.20	+2.66
7	0	+0.64	+2.06	+2.31

3. Conclusions

On the basis of the above results, we can conclude that both, L-proline catalysed Claisen–Schmidt aldol condensation and Knoevenagel reaction, are very appropriate ways for the stereocontrolled transformation of the aldehyde function of complex polyfunctionalised molecules into a 1-hydroxy-3-oxobutyl moiety.

4. Experimental

4.1. General

Solutions were dried over $MgSO_4$ before concentration under reduced pressure. The ^1H and ^{13}C NMR spectra were recorded with Bruker AMX-300, AM-300, and ARX-400 spectrometers for solutions in $CDCl_3$ (internal Me_4Si). IR spectra were recorded with a Perkin–Elmer 782 instrument and mass spectra with a Micromass Mod. Platform II and Autospec-Q mass spectrometers. Optical rotations were measured for solutions in $CHCl_3$ (1 dm tube) with a Jasco DIP-370 polarimeter. GLC was performed on a Hewlett–Packard 6890 gas chromatograph equipped with split/splitless injector, a flame-ionisation detector, and a capillary HP-5 column (30 m×0.25 mm i.d.×0.25 m film thickness) at: (A) 5 min at 180°C, program to 250°C, 10°C/min; (B) 5 min at 200°C, program to 250°C, 10°C/min; (C) 6 min at 180°C, program to 240°C, 15°C/min. The He flow rate was 1.1 mL/min, the injection port and the zone-detector temperatures were 275°C (A, B), and 250°C (C). TLC was performed on precoated silica gel 60 F_{254} aluminium sheets and detection by charring with H_2SO_4. Column chromatography was performed on silica gel (Merck, 7734).

4.2. (*E*)-1,3,4-Trideoxy-5,6:7,9-di-*O*-isopropylidene-α-L-*xylo*-non-3-ene-2,5-diulo-5,8-furanose 10

To a stirred solution of **7**[2] (52 mg, 0.2 mmol) in dry dichloromethane (2 mL) was added 1-phosphoranylidene-2-propanone (120 mg, 0.4 mmol) and the mixture was stirred at room temperature for 2 days. GLC (*A*) then revealed the presence of a new main component. The reaction mixture was concentrated and the residue chromatographed (ether–hexane, 1:4→1:2) to afford crystalline **10** (33 mg, 55%); mp 87–88°C (from ether–hexane); R_t 9.06 min (A); $[\alpha]_D^{26}$ +24 (*c* 1); ν_{max}^{KBr} 1682 (C=O, ketone), 1388 and 1378 cm^{-1} (CMe_2). For NMR data, see Tables 2 and 3. Anal calcd for $C_{15}H_{22}O_6$: C, 60.39; H, 7.43. Found: C, 60.69; H, 7.17%.

4.3. Typical experimental procedure for the catalytic asymmetric aldol reaction of acetone and 'diacetone hexulose aldehydes' 2 and 7

L- or D-Proline (50 mg, 0.43 mmol) in DMSO/acetone (4:1, 5 mL) was sonicated for 15 min. A solution of aldehyde **2**[1] or **7** (0.9–1.4 mmol) in the same solvent (5 mL) was added and the mixture was stirred until the starting **2** or **7** had disappeared (36 h to 10 days). The reactions were monitored by GLC analysis (A). The mixture was treated with saturated aqueous ammonium chloride solution (10 mL) and extracted with ether (3×20 mL). The combined extracts were concentrated and the residue submitted to chromatography (ether–hexane, 2:3→1:1) to afford, in the case of using L-proline, the corresponding pure β-hydroxyketones **3** and **8**, respectively. When D-proline was the chiral catalyst compounds **3** and **4** were isolated in pure state, but unfortunately **8** and **9** could not be resolved.

1,3-Dideoxy-5,6:7,8-di-*O*-isopropylidene-β-D-*manno*-non-2,5-diulo-5,9-pyranose 3: R_t 7.60 min (*B*); $[\alpha]_D^{26}$ +1.7, $[\alpha]_{405}^{25}$ +12 (*c* 1.2); ν_{max}^{film} 3486 (OH), 1716 (C=O, ketone), and 1384 cm^{-1} (CMe_2). For NMR data, see Tables 2 and 3. Mass spectrum (LSIMS): *m*/*z*: 339.1418 [M^++Na] for $C_{15}H_{24}O_7Na$ 339.1420 (deviation 0.4 ppm).

1,3-Dideoxy-5,6:7,8-di-*O*-isopropylidene-β-D-*gluco*-non-2,5-diulo-5,9-pyranose 4: R_t 8.57 min (B); $[\alpha]_D^{26}$ −18, $[\alpha]_{405}^{27}$ −32 (*c* 1.7); ν_{max}^{film} 3491 (OH), 1717 (C=O, ketone), and 1383 cm^{-1} (CMe_2). For NMR data, see Tables 2 and 3. Mass spectrum (LSIMS): *m*/*z*: 339.1415 [M^++Na] for $C_{15}H_{24}O_7Na$ 339.1420 (deviation 1.4 ppm).

1,3-Dideoxy-5,6:7,9-di-*O*-isopropylidene-α-L-*gulo*-non-2,5-diulo-5,8-furanose 8: R_t 9.30 min (A); $[\alpha]_D^{27}$ +15 (*c* 1.1); ν_{max}^{film} 3504 (OH), 1713 (C=O, ketone), 1382 and 1374 cm^{-1} (CMe_2). For NMR data, see Tables 2 and 3. Mass spectrum (LSIMS): *m*/*z*: 339.1415 [M^++Na] for $C_{15}H_{24}O_7Na$ 339.1420 (deviation 1.3 ppm).

4.4. Typical procedure for Knoevenagel reaction of aldehydes 2 and 7 with acetoacetic acid

To a cooled solution of aldehyde **2** or **7** (1.8 mmol) in toluene (10 mL) was added a cooled solution of acetoacetic acid[10] (2–2.6 mmol) in 1:1 toluene–ether (10 mL) and diethylamine (0.2 mL) and the mixture left at room temperature for 48 h–4 days. The progress of the reaction was monitored by GLC analysis. The reaction mixture was supported on silica gel and chromatographed (ether–hexane, 2:3) to afford either **3** (500 mg) or **8** (380 mg), respectively.

4.5. Typical procedure for Reformatsky reaction of aldehydes 2 and 7 with bromoacetone

To a solution of aldehyde **2** or **7** (1.2–1.4 mmol) in anhydrous dioxane (4 mL) was added bromoacetone (1.5–2.4 mmol), zinc dust (170–200 mg) and iodine (80 mg), and the resulting suspension was sonicated for 2–8 h. The progress of the reaction was monitored by GLC analysis. The reaction mixture was treated with satu-

rated aqueous ammonium chloride (10 mL) and extracted with ether (3×10 mL). The combined extracts were concentrated and submitted to chromatography (ether–hexane, 1:3→1:1) to yield, in the case of aldehyde **2**, the α,β-enone **5** [33 mg, R_t 7.31 min (B)], which optical and spectroscopic data were identical to those previously reported[7] and β-hydroxyketone **3** (106 mg). In the second case (aldehyde **7**) the α,β-enone **10** (63 mg) and β-hydroxyketone **8** (150 mg), slightly contaminated with its 4*S*-epimer **9**, were isolated.

4.6. Degradation of hydroxyketones 3 and 8

(a) To a freshly prepared aqueous 0.4 M sodium hypobromite solution (8 mL) was added compound **3** (430 mg, 1.36 mmol) and the mixture sonicated for 2 h. The reaction mixture was extracted with ether and the aqueous layer was acidified (pH 3) with 6N aqueous hydrochloric acid and then extracted with ether (5×10 mL). The combined extracts were concentrated and the residue dissolved in methanol (10 mL) and treated with a stream of diazomethane until a faint yellow solution was obtained. The reaction mixture was left at room temperature for 30 min and then GLC analysed (C), showing the presence of a main component with the same R_t (9.80 min) to that showed by an authentic sample of β-hydroxy ester **11**.[5d]

(b) Compound **8** (276 mg, 0.9 mmol) was degraded as above to afford β-hydroxyester **12**[5d] as indicated by the corresponding GLC analysis (C).

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