Resolution and Asymmetric Synthesis of 3-Hydroxycarboxylic Acids by using (−)-Menthone as a Chiral Template

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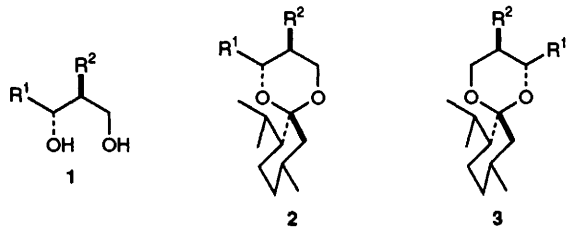
1,3-Dioxan-4-ones **6** and **7** derived from (−)-menthone can be utilized in resolution of 3-hydroxycarboxylic acids and asymmetric synthesis of 2-substituted 3-hydroxycarboxylic acids.

By acetalization with (−)-menthone, enantiomeric alkane-1,3-diols **1** and *ent*-**1** are converted into diastereoisomeric menthonides **2** and **3**, respectively, which can be separated readily by silica gel column chromatography. Recent reports from these laboratories demonstrated that the transformation can be utilized in resolution of the racemic 1,3-diols,[1] determination of the absolute configuration of the 1,3-diols,[1] and enantioselective terminus differentiation of *meso*-1,3-polyols.[2] As an extension of this approach using menthone as a chiral template, we have investigated the condensation of racemic 3-hydroxycarboxylic acids with (−)-menthone.[3] We now report resolution of 3-hydroxycarboxylic acids *rac*-**4** *via*

Table 1 Resolution of 3-hydroxycarboxylic acids **4a–c**

Entry	*rac*-4	R^1	*rac*-5	Yield[a] (%)	6,7	Yield[b] (%)	R_f[c]	4, *ent*-4	Yield[b] (%)	($CHCl_3$, *c*)
1	**4a**	*c*-C_6H_{11}	**5a**	79	**6a**	39	0.41	**4a**	88	−29.0 (1.41)
					7a	30	0.49	*ent*-**4a**	96	+30.4[d] (1.03)
2	**4b**	$PhCH_2CH_2$	**5b**	90	**6b**	41	0.25	**4b**	83	+14.0 (1.04)
					7b	34	0.34	*ent*-**4b**	76	−14.5 (1.02)
3	**4c**	*n*-C_8H_{17}	**5c**	82	**6c**	40	0.44	**4c**	93	−18.5[e] (0.73)
					7c	37	0.53	*ent*-**4c**	88	+18.3 (0.74)

[a] Isolated yield by distillation. [b] Isolated yield by column chromatography (silica gel, EtOAc–hexane). [c] Retardation factor (silica gel, 15% EtOAc–hexane). [d] Lit;[9] $[\alpha]_D$ +31.8 ($CHCl_3$, *c* 1.1). [e] Lit.,[10] $[\alpha]_D$ −17 ($CHCl_3$, *c* 1).



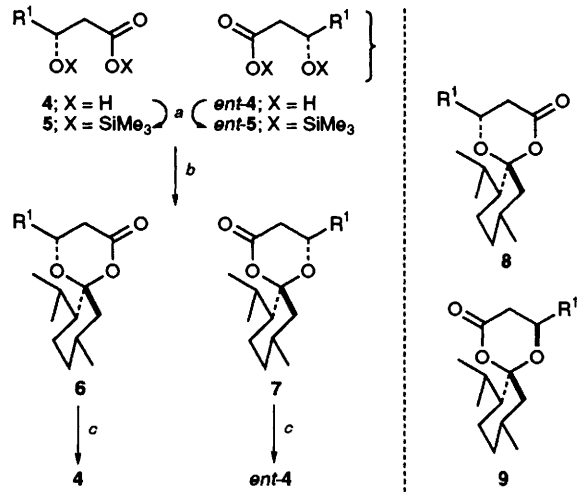
the (−)-menthone-derived 1,3-dioxanones **6** and **7** and asymmetric synthesis of 2-substituted 3-hydroxycarboxylic acids by highly stereoselective alkylation and aldol reactions of **6** and **7**.

Hydroxycarboxylic acids *rac*-**4a–c** were converted into the bistrimethylsilyl ether derivatives *rac*-**5** in high yields by treatment with hexamethyldisilazane (HMDS) (Scheme 1, Table 1). Condensation of *rac*-**5** with (−)-menthone catalysed by trimethylsilyl trifluoromethanesulfonate (TMSOTf) gave 1,3-dioxanones **6**, derived from **5**, and 1,3-dioxanones **7**, derived from *ent*-**5**, without formation of the possible diastereoisomers, **8** and **9**. The dioxanones **6–9** assume chair-like conformations **6′–9′**. Flipping of the dioxanone rings is restricted by the isopropyl group of the menthane ring. Formation of **8** and **9** in which the R group takes a pseudo-axial position is highly unfavourable.

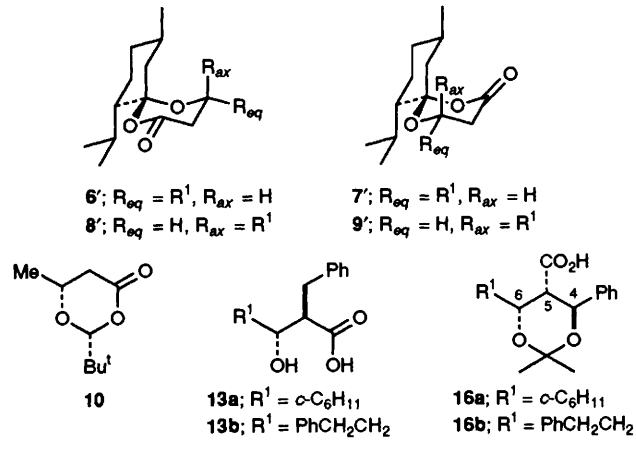
The diasteroisomeric 1,3-dioxanones **6a–c** and **7a–c** were readily separated by silica gel column chromatography. The enantiomerically pure hydroxycarboxylic acids **4a–c** and *ent*-**4a–c** were obtained by acid-catalysed hydrolysis of **6a–c** and **7a–c**, respectively. Separation of the hydroxy acids and (−)-menthone liberated was achieved readily by extraction.

Recent studies by Seebach and coworkers disclosed that 2-*tert*-butyldioxanone **10** prepared from enantiomerically pure 3-hydroxybutanoic acid and pivalaldehyde is a versatile intermediate for the synthesis of enantiomerically pure compounds.[4–7] It was reported that alkylation[5] and aldol reactions[6] of **10** proceed with high *anti*-selectivity to give, after hydrolysis, the corresponding enantiomerically pure 2-substituted hydroxycarboxylic acids. Structurally related dioxanones **6** and **7** were found to exhibit distinctive stereoselectivities in alkylation and aldol reactions.

Treatment of the lithium enolates of **6a,b** and **7a,b** with benzyl and allyl bromides stereoselectively gave the corresponding *anti*-products *a*-**11** and *a*-**12**,† respectively [eqns. (1) and (2); Table 2]. Interestingly, reversal of the selectivity was observed in the reaction with methyl iodide, which yielded the corresponding methylation products *s*-**11** and *s*-**12**† with



Scheme 1 *Reagents and conditions*: *a*, HMDS (1.1 equiv.), CH_2Cl_2, room temp., 18 h; *b*, (−)-menthone (1.5–2.0 equiv.), TMSOTf (0.2 equiv.), CH_2Cl_2, −40 °C, 18 h; *c*, aq. HCl, MeOH, room temp., 1 h



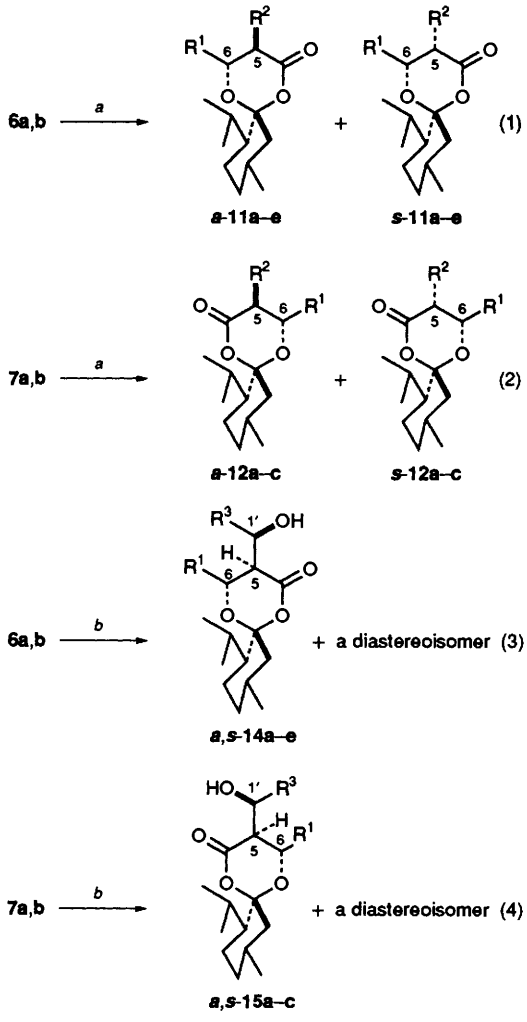
moderate *syn*-selectivity. The *syn*-selectivity was improved in the methylation of the corresponding potassium enolates (entries 4 and 7 *vs.* 5 and 8). While the origin of the reversed stereoselectivity is not apparent, the observation is of synthetic importance as a rare example of *syn*-selective alkylation of 3-hydroxycarboxylic acid derivatives.[8] Treatment of the alkylation products **11a,d** and **12a,c** with aq. HCl in MeOH furnished the corresponding enantiomerically pure

† Alkylation products *a*- and *s*-**11** (*a*- and *s*-**12**) were separated by silica gel column chromatography. The stereochemistry of these compounds was determined based on the vicinal coupling constants $J_{5,6}$; 9.5–10.6 Hz for *a*-**11** and -**12**, 2.5–3.3 Hz for *s*-**11** and -**12**.

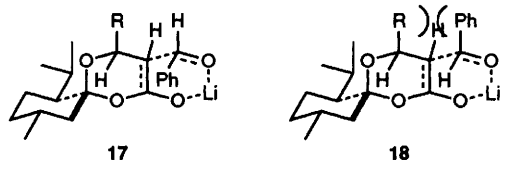
Table 2 Alkylation and aldol reaction of dioxanones **6a,b** and **7a,b**[a]

Entry	Dioxanone	Base	R^2X or R^3CHO	Products	Yield[b] (%)	Ratio[c]
1	**6a**	LDA	$PhCH_2Br$	***a*-11a, *s*-11a**	71	>20:1
2		KHMDS			63	9.5:1[d]
3		LDA	$CH_2{=}CHCH_2Br$	***a*-11b, *s*-11b**	74	13:1[d]
4		LDA	MeI	***a*-11c, *s*-11c**	91	1:2.2
5		KHDS			85	1:7.3[d]
6	**7a**	LDA	$PhCH_2Br$	***a*-12a, *s*-12a**	84	>20:1
7		LDA	MeI	***a*-12b, *s*-12b**	77	1:1.3
8		KHDS			83	1:3.4[d]
9	**6b**	LDA	$PhCH_2Br$	***a*-11d, *s*-11d**	55	>20:1
10		LDA	MeI	***a*-11e, *s*-11e**	73	1:2.0
11	**7b**	LDA	$PhCH_2Br$	***a*-12c, *s*-12c**	47	>20:1
12	**6a**	LTMP	PhCHO	***a,s*-14a**	87	8.7:1
13	**7a**	LTMP	PhCHO	***a,s*-15a**	88	11:1
14	**6b**	LTMP	PhCHO	***a,s*-14b**	80	10:1
15	**7b**	LTMP	PhCHO	***a,s*-15b**	76	>20:1
16		LTMP	$CH_2{=}C(Me)CHO$	***a,s*-15c**	60	15:1

[a] In the alkylation reaction, the enolates generated from 1.2–1.5 equiv. of lithium diisopropylamide (LDA) or potassium hexamethydisilylamide (KHDS) in tetrahydrofuran–hexamethylphosphoric triamide (2.4 equiv.) at −75 °C for 2 h were allowed to react with R^2X (1.2–1.5 equiv.) at −75 °C for 16 h. In the aldol reactions, the enolates generated from 1.2 equiv. of lithium tetramethylpiperidide (LTMP) at −75 °C for 2 h were treated with R^3CHO (1.2 equiv.) at temperatures of −75 to −10 °C for 2 h. [b] Combined yields of stereoisomers. [c] Unless otherwise noted ratios were determined by ^1H NMR analysis. [d] The ratio was determined by isolation.



Scheme 2 *Reagents and conditions*: *a*, LDA, THF, HMPA, −75 °C, then R^2X, −75 °C; *b*, LTMP, THF, −75 °C, then R^3CHO, −75 °C



2-substituted 3-hydroxycarboxylic acids **13a,b** and *ent*-**13a,b**, respectively.‡

Aldol reaction of **6a,b** (or **7a,b**) also proceeded with high stereoselectivity to give ***a,s*-14** (or ***a,s*-15**) as a major product together with a minor diastereoisomer [eqns. (3) and (4); Table 2]. The stereochemistry of the major products was unambiguously determined by converting them into acetonide derivatives **16**. Thus, hydrolysis of ***a,s*-14a**, **-14b** and **-15b** with aq. HCl in MeOH followed by protection of the 1,3-diol moieties as acetonides [$Me_2C(OMe)_2$, camphorsulfonic acid, CH_2Cl_2] gave **16a** (82%, $J_{4,5}$ = 9.0, $J_{5,6}$ = 6.3 Hz), **16b** (60%, $J_{4,5}$ = 9.0, $J_{5,6}$ = 6.3 Hz), and *ent*-**16b** (92%), respectively.§ As in the reaction of **10**,[6] aldehydes attack stereoselectively from the *anti* π-face of the enolates. Noteworthy is the *syn*-selective [with respect to C(5) and C(1′)] aldol reaction, which contrasts with the *anti*-selectivity reported for **10**.[6] Unfavourable 1,3-interaction between the R^1 and R^3 groups in the cyclic transition state model **18** leading to ***a,a*-14** may provide a rationalisation of the highly stereoselective formation of ***a,s*-12** through the sterically more feasible transition state model **17**.

In summary, we have demonstrated that transformation of racemic 3-hydroxycarboxylic acids into dioxanones **6** and **7** can be utilized not only in resolution of the starting hydroxycarboxylic acids but also in asymmetric synthesis of 2-substituted hydroxycarboxylic acid derivatives. Stereoselectivities

‡ **13a** {84%, $[\alpha]_D^{24}$ −14.4 ($CHCl_3$, *c* 0.98)}, **13b** {77%, $[\alpha]_D^{24}$ −23.5 ($CHCl_3$, *c* 0.77)}, *ent*-**13a** {79%, $[\alpha]_D^{24}$ + 15.3 ($CHCl_3$, *c* 1.2)}, *ent*-**13b** {81%, $[\alpha]_D^{24}$ + 24.5 ($CHCl_3$, *c* 0.99)}.

§ The *anti*-stereochemistry of ***a,s*-14a–c** and **-15a,b** at C(5) was assigned on the basis of the vicinal coupling constants; $J_{5,6}$ = 9.2–10.0 Hz.

observed in alkylation and aldol reactions of the enolates derived from dioxanones **6** and **7** are markedly different from those observed for the related 2-*tert*-butyldioxanone **10**.

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