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Enantioselective Synthesis of α-Hydroxy Acids Employing (1*S*)-(+)-*N*,*N*-Diisopropyl-10-camphorsulfonamide as Chiral Auxiliary

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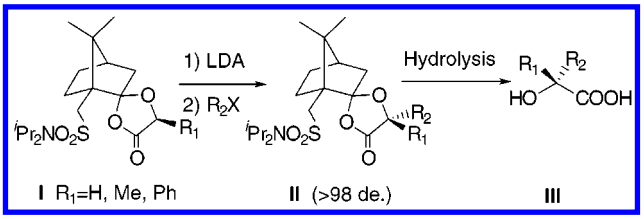
ABSTRACT



Lewis acid (BF_3·OEt_2) catalyzed condensation of dimethoxy acetal 2 with α-hydroxy acids produces chiral 1,3-dioxolanones I. The enolates derived from these compounds undergo reactions with alkyl halides with a high level of diastereoselectivity. Subsequent hydrolysis of these alkylated products II gives mono- and disubstituted α-hydroxy acids III with high enantiomeric excesses.

Optically active α-hydroxy acids are structural subunits of many natural products, such as motuporin,[1a] integerrimine,[1b] monocrotaline,[1c] and eremantholide A.[1d] In addition, α-hydroxy acid derivatives are important intermediates for asymmetric synthesis.[2] A number of useful synthetic methods for the preparation of enantiomertically pure α-branched α-hydroxy acids have been developed.[3] However, the need for development of a more efficient method still exists. Herein we report an enantioselective synthetic method for mono- and disubstituted α-hydroxy acids from glycolic acid, lactic acid, and mandelic acid, employing (1*S*)-(+)-*N*,*N*-diisopropyl-10-camphorsulfonamide **1** as a chiral auxiliary.[4]

Under the conditions of Farines[5] or Pearson,[6] condensation of **1** with glycolic acid either did not give the expected chiral 1,3-dioxolanone or gave it in low yield. However, Lewis acid (BF_3·OEt_2) catalyzed condensation of dimethoxy acetal

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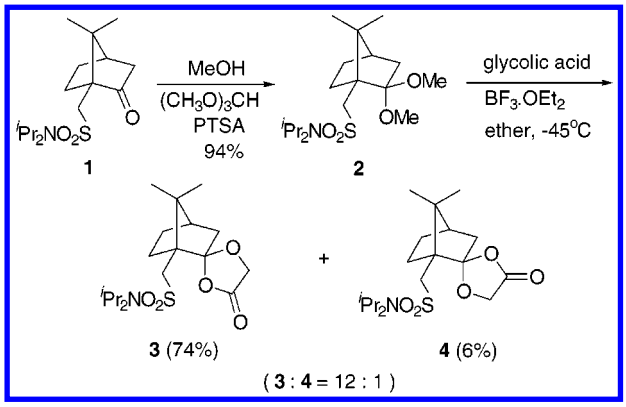
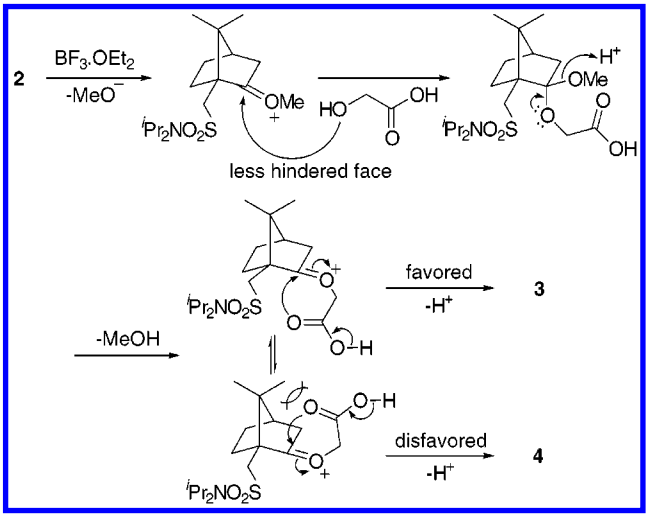
2, derived from **1**, with glycolic acid at −45 °C in diethyl ether produced diastereomeric chiral 1,3-dioxolanones **3** and **4** in a 12:1 ratio (Scheme 1). Pure **3** could be obtained by

Scheme 1



recrystallization or separated from the minor isomer **4** by column chromatography. The stereochemistries of **3** and **4** were tentatively assigned on the basis of a plausible mechanism for the condensation of dimethoxy acetal **2** with glycolic acid (Scheme 2).

Scheme 2



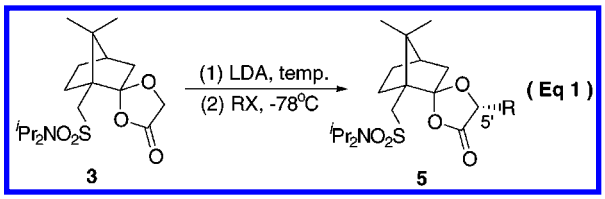
Treatment of **3** with lithium diisopropylamide (LDA) in tetrahydrofuran (THF) at −78 °C and in the presence of hexamethylphosphoramide (HMPA) followed by alkyl halide gave the corresponding alkylation product in good yield (Table 1, eq 1). The diastereoselectivities are 93.5% to

Table 1. Alkylation of Dioxolanone **3**

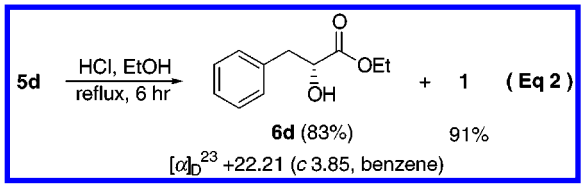
no.	additive	R	temp (°C)	product	yield (%)	de (%)[a]	confgn (C_5')
1	HMPA	CH_3	−78	**5a**	77	93.5 (30:1)	*R*
2			−100→−78	**5a**	84	>98	*R*
3	HMPA		−100→−78	**5a**	86	>98	*R*
4		CH_2=$CHCH_2$	−100→−78	**5b**	76	>98	*R*
5	HMPA		−100→−78	**5b**	83	>98	*R*
6	HMPA	Et	−78	**5c**	36[b]	>98	*R*
7	HMPA		−100→−78	**5c**	65	>98	*R*
8	HMPA	$PhCH_2$	−78→−45	**5d**	60	>98	*R*
9	HMPA		−100→−78	**5d**	70	>98	*R*

[a] No second isomer has been detected by 400 MHz ^{1}H NMR spectroscopy. [b] 57% yield of **1** was recovered.

>98%, as judged from their ^{1}H NMR spectra (Table 1, entries 1, 6, and 8). On the basis of our previous experience,[7]



the major product presumably arose from the alkylation of the enolate on the less hindered *si* face. When deprotonation and addition of alkyl halide were conducted at −100 °C and then the solution was warmed to −78 °C, the diastereoselectivities and the yields could be improved. In fact, the minor diastereoisomers could not be detected by 400 MHz ^{1}H NMR measurement under the improved experimental procedure. Ethanolysis of the benzylated product **5d** was achieved by heating **5d** with anhydrous hydrogen chloride in ethanol to give (*R*)-ethyl glycolate **6d**,[3a,8] and chiral auxiliary **1** was recovered in high yield (eq 2).



Attempts to quarternize the α-carbon of the glycolic acid were studied. To extend the scope of this methodology, racemic α-substituted α-hydroxy acids reacted with dimethoxy acetal **2**. On condensation of dimethoxy acetal **2** with *rac*-lactic acid, compound **7a** was isolated as a single product (eq 3). Optimization of the reaction conditions revealed that an excess of *rac*-lactic acid was necessary for a more efficient conversion. On the other hand, compound **7b** could be obtained as a single product from condensation of *rac*-mandelic acid with **2**. The stereochemistries of **7a** and **7b**

(4) (a) Po, S.-Y.; Hung, S.-C.; Liu, H.-H.; Hsu, C.-Y.; Lin, S.-L.; Chang, J.-W.; Uang, B.-J. *Pure Appl. Chem.* **1997**, *69*, 615. (b) Chang, S.-W.; Hung, C.-Y.; Liu, H.-H.; Uang, B.-J. *Tetrahedron*: *Asymmetry* **1998**, *9*, 521.

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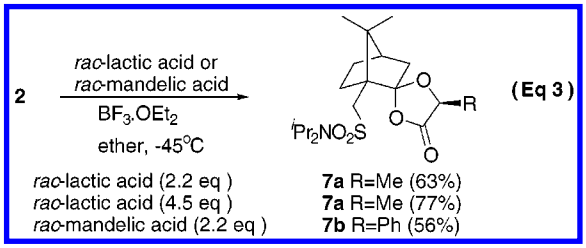
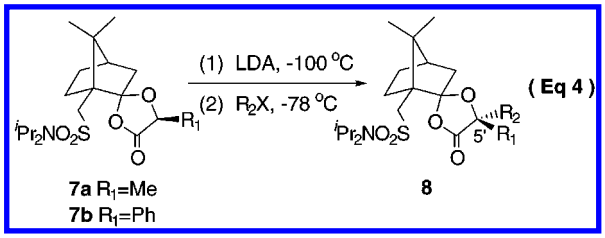
(8) Optical rotation for **6d**: $[\alpha]^{23}_D$ +22.21 (*c* 3.85, benzene), lit.[3a] (*R*)-**6d**, $[\alpha]^{25}_D$ +21.40 (*c* 0.43, benzene), lit.[9] $[\alpha]^{18}_D$ +22.50 (*c* 3.98, benzene).



were confirmed by X-ray crystallographic analysis for **7a** and NOE experiments for **7b**. Interestingly, the stereochemistry at the α-carbons of both **7a** and **7b** is *S*. Compounds **7a**,**b** are presumably the thermodynamically more stable products.

We then examined the alkylation of **7a** and **7b** with alkyl halides. Treatment of either **7a** or **7b** with LDA at −100 °C



followed by the addition of alkyl halide gave the corresponding product with excellent diastereoselectivity (Table 2, eq 4). Compounds **8a**,**d**,**g** were hydrolyzed in methanol

Table 2. Alkylation of Dioxolanones **7a** and **7b**

no.	R_1	R_2	product	yield (%)	de (%)[a]	confgn (C_5')
1	Me	CH_3CH_2	**8a**	79	>98	*R*
2	Me	$CH_3CH_2CH_2$	**8b**	67	>98	*R*
3	Me	CH_2=$CHCH_2$	**8c**	78	>98	*R*
4	Me	$CH_3CH_2CH_2CH_2$	**8d**	74	>98	*R*
5	Me	$C_6H_5CH_2$	**8e**	82	>98	*R*
6	Ph	CH_3	**8f**	76	>98	*S*
7	Ph	CH_2=$CHCH_2$	**8g**	84	>98	*S*

[a] No second isomer was detected by 400 MHz ^{1}H NMR spectroscopy.

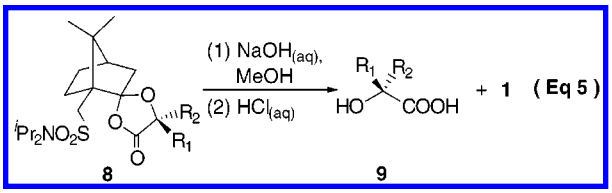
with 2 N $NaOH_{aq}$ followed by acidification to give the corresponding optically pure α-hydroxy acids **9**, and chiral auxiliary **1** was recovered in high yield (Table 3, eq 5).[3b,10] The stereochemistry of **8** was unambiguously assigned on the basis of the X-ray crystallographic analysis of **8a** and

Table 3. Hydrolysis of Dioxolanones **8a**, **8d**, and **8g**

product	R_1	R_2	yield (%)	recovery of **1** (%)	$[\alpha]_D$	confgn
9a	Me	Et	97	96	−7.03 (*c* 1.4, 0.2 N NaOH)[a]	*R*
9d	Me	Bu	98	92	−8.12 (*c* 0.85, H_2O)[a]	*R*
9g	Ph	allyl	94	93	+29.54 (*c* 1.0, $CHCl_3$)[a]	*S*

[a] See ref 11.

by comparison of the ^{1}H NMR spectra with that of the products obtained from hydrolysis of compounds **8a**,**d**,**g**. These results suggested that alkylation of **7a** proceeded from the less hindered *si* face as expected. Treatment of **5a** with LDA at −100 °C followed by the addition of ethyl iodide gave a single product in 78% yield. The spectral data of this product were identical with those obtained from **8a**. Thus, **5a** and **7a** are C_5' epimers that gave identical enolates upon treatment with LDA. It also implies that the assignments of the stereochemistry for **3**, **4**, and **5** are correct.



In conclusion, we have developed an efficient method for the preparation of α-hydroxy acids with high stereoselectivity by employing **1** as a chiral auxiliary. The alkylated products were hydrolyzed to give the corresponding α-hydroxy acids without racemization and recovery of the chiral auxiliary in an efficient manner.

Acknowledgment. This work was supported by the National Science Council of the Republic of China.

Supporting Information Available: Detailed experimental procedures, NMR spectral data for new compounds, NOE spectral data for **7b**, and X-ray analysis data for **7a** and **8a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) Optical rotation: lit.[3b] (*R*)-**9a**, $[\alpha]^{25}_D$ −6.6 (*c* 1.4, 0.2 N NaOH); lit.[9a] (*R*)-**9b**, $[\alpha]^{24}_D$ −7.75 (*c* 0.85, H_2O); lit.[9b] (*S*)-**9g**, $[\alpha]^{22}_D$ +29.0 (*c* 1.0, $CHCl_3$).