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SYNTHESIS OF OPTICALLY ACTIVE α-ALKYL THIOGLYCOLIC ACID DERIVATIVES[1]

Hung-Hsin Liu, Erh-Ning Chen, Biing-Jiun Uang* and Sue-Lein Wang

Department of Chemistry, National Tsing Hua University

Hsinchu, Taiwan 30043, Republic of China

Summary : A synthetic method equivalent to an enantioselective alkylation of thioglycolic acid to optically active α-alkylated thioglycolic acids via an optically active 1,3-oxathiolan-5-one intermediate is described.

The synthesis of optically active α-substituted thioglycolic acids has been reported in recent years, which involves a self-reproduction of chirality from an optically active α-monosubstituted thioglycolic acid,[2] or reaction of thiolates with an optically active α-heterosubstituted acetic acid.[3] Herein we wish to report a synthetic method for the preparation of optically active α-substituted thioglycolic acid from thioglycolic acid with the assistance of chiral auxiliary molecule.

When a benzene solution containing (R)-(+)-camphor (1eq) and thioglycolic acid (1.1eq) in the presence of a catalytic amount of p-toluenesulfonic acid was refluxed for 120 hours, two optically active oxathiolanones **1a**[4] and **1b**[4] were obtained in a ratio of 5.6 to 1 with a total yield 95% (conversion 52%).[5] The preferential formation of 1,3-oxathiolan-5-one **1a** would be predicted by an endo attack on carbonyl carbon of camphor by the more nucleophilic sulfur atom of the thioglycolic acid, followed by a lactonization (scheme). These two isomeric oxathiolanones were separable by a preparative HPLC. The major oxathiolanone **1a** was deprotonated with lithium diisopropylamide (1 eq) in THF at -78°C and alkylated with a variety of alkyl halides (1 eq) at appropriate temperature in good yield with excellent diastereoselectivity (Table). The major isomer presumably was obtained by an alkylation of the enolate from the less hindered face. The predicted stereochemistry of ketalization and alkylation were in agreement with the x-ray crystallography result.[6] It had been mentioned that direct alkylation at C_4 on C_4 unsubstituted 2,2-dimethyl-1,3-oxathiolan-5-one was difficult.[7] However, monoalkylation at C_4 on C_4 unsubstituted 1,3-oxathiolan-5-one **1a** could be easily achieved in our case by selecting suitable reaction condition or electrophile.

Treatment of **2a** in refluxing ethanolic hydrogen chloride for 18 hours liberated (S)-ethyl α-methyl thioglycolate[8] in 88% yield and recovered 94% camphor. Treatment of **2a'** under the same reaction condition liberated (R)-ethyl α-methylthioglycolate[9] in 90% yield. The stereochemical assignments for **1a** and **1b** were again confirmed by this

chemical correlation.

In a typical experiment, 1,3-oxathiolan-5-one **1a** (2.50 mmol) in THF (5 ml) was dropwise added to a solution of LDA (2.50 mmol) in THF (25 mL) at -78°C. After 30 min, alkyl holide (2.50 mmol) was dropwise added in 2 min at -78°C or -40°C, and the solution was stirred for an additional period of time as indicated in table. Oxalic acid (5% aqueous solution) was carefully added to neutralize the above solution, and the mixture was extracted three times with ethyl acetate. The combined organic layer was dried with anhydrous sodium sulfate and concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2; ethyl acetate-hexanes 1:20) to give a mixture of **2** and **2'**. The mixture of **2** and **2'** was further purified by preparative HPLC (SiO_2, 7μm; ethyl acetate-hexanes 1:60) to afford pure **2** and pure **2'**. A solution of **2a** or **2a'** (0.08M) in anhydrous ethanol, containing 2 eq anhydrous hydrochloric acid, was refluxed for 18 hours. After cooling, the mixture was diluted with dichloromethane and neutralized with cold sodium bicarbonate solution. The organic layer was dried over anhydrous sodium sulfate, then was concentrated *in vacuo*. Purification of the residue by column chromatography afforded **3** (bp 75°C/15 mmHg)[3a] and recovered R-(+)-camphor.

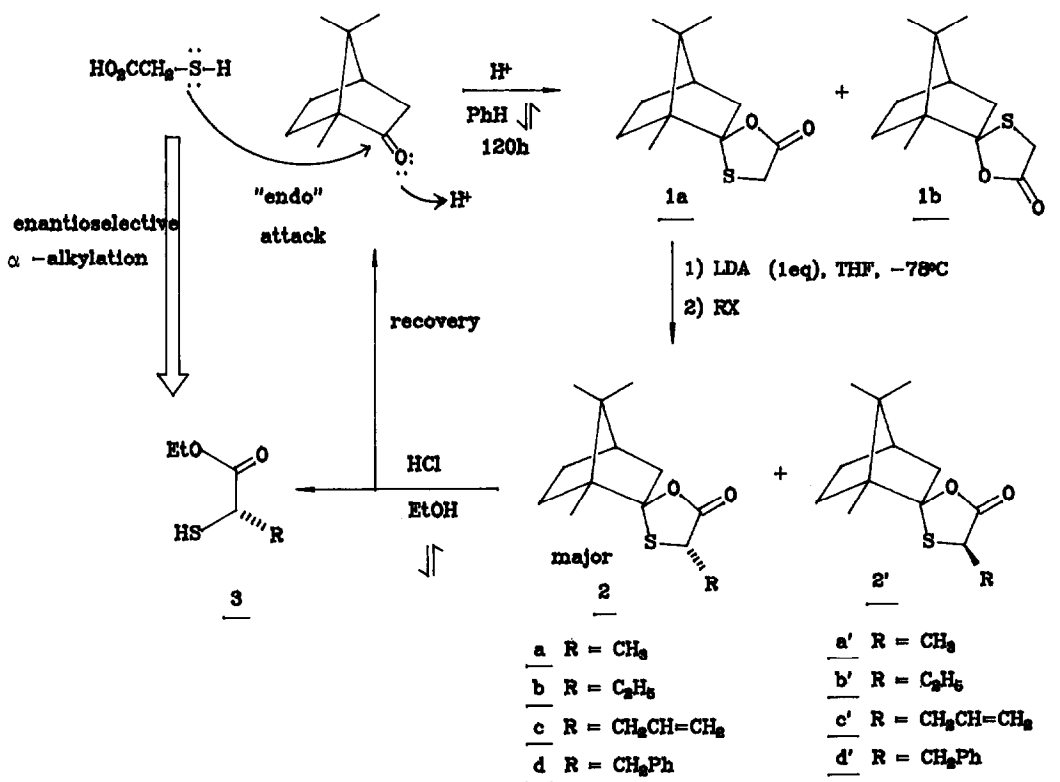

Table: Alkylation of The Major 1,3-Oxathiolane-5-one 1a

entry	RX	reaction condition	yield	ratio 2/2'[4]
1	CH_3I	−78°C 20min	>95%	13:1
2	C_2H_5I	−78°C 1hr	no reaction	
3	C_2H_5I	−40°C 30min	70%	13:1
4	CH_2=CH−CH_2I	−78°C 1hr	89%	104:1
5	CH_2=CH−CH_2Br	−78°C 1hr	62%	60:1
6	CH_2=CH−CH_2Br	−40°C 30min	85%	75:1
7	$PhCH_2I$	−78°C 1hr	88%	156:1
8	$PhCH_2Br$	−78°C 1hr	71%	98:1

In summary, a synthetic method for the enantioselective alkylation of thioglycolic acid has been demonstrated. However, we encountered a separation problem which required a preparative HPLC for the separation of diastereomers. Search for a better chiral auxiliary molecule is currently underway and the result will be reported in due course.

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References and Notes

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   (b) Strijtveen, B.; Kellogg, R. M. *Recl. Trav. Chim, Pays-Bas*, **1987**, *106*, 539.
4. **1a** ^{1}H NMR δ ($CDCl_3$, 400MHz) 3.60(d, J=16.36Hz, 1H), 3.48 (d, J=16.36Hz, 1H), 0.96 (s, 3H), 0.83 (s, 6H), 1.05~1.12 (m, 1H), 1.48~1.53 (m, 2H), 1.63~1.68 (m, 1H), 1.77 (t, J=4.24 Hz, 1H), 1.89 (d, J=14.3Hz, 1H), 2.48~2.54 (ddd, J=14.3Hz, 4.24Hz, 3.45Hz, 1H); $[\alpha]_D^{23}$ +7.7° (C=4, EtOAc). **1b** ^{1}H NMR δ ($CDCl_3$, 400MHz) 3.65 (d, J=17.39Hz, 1H), 3.61 (d, J=17.39Hz, 1H), 1.03 (s, 3H), 0.95 (s, 3H), 0.90 (s, 3H), 1.28~2.42 (m, 7H). **2a** ^{1}H NMR δ ($CDCl_3$, 400MHz) 3.86 (q, J=7.06Hz, 1H), 2.60~2.66 (m, 1H), 1.90 (d, J=14.24Hz, 1H), 1.81 (t, J=4.44Hz, 1H), 1.71~1.62 (m, 2H), 1.57

(d, J=7.06Hz, 3H), 1.51~1.54 (m, 1H), 1.10~1.15 (m, 1H), 1.04 (s, 3H), 0.89 (s, 3H), 0.88 (s, 3H); $[\alpha]_D^{23}$ -1.65° (C=10, EtOAc). **2a'** ^{1}H NMR δ ($CDCl_3$, 400MHz) 3.93 (q, J=7.12Hz, 1H), 2.52~2.58 (m, 1H), 2.05 (d, J=13.8Hz, 1H), 1.85 (t, J=4.52Hz, 1H), 1.70~1.80 (m, 1H), 1.41~1.46 (m, 1H), 1.03~1.50 (m, 1H), 1.53(d, J=7.12Hz, 3H), 1.03 (s, 3H), 0.92 (s, 3H), 0.90 (s, 3H); $[\alpha]_D^{23}$ +5.8° (C=2, EtOAc). **2b** ^{1}H NMR δ ($CDCl_3$, 400 MHz) 3.76 (dd, J=4.84Hz, 4.80Hz, 1H), 2.57~2.62 (m, 1H), 2.03~2.10 (m, 1H), 1.91 (d, J=14.24Hz, 1H), 1.63~1.82 (m, 3H), 1.10~1.17 (m, 1H), 1.05 (t, J=7.36Hz, 3H), 1.04 (s, 3H), 0.89 (s, 3H), 0.88 (s, 3H); $[\alpha]_D^{27}$ -4° (C=1, $CHCl_3$). **2b'** ^{1}H NMR δ ($CDCl_3$, 400MHz) 3.90 (dd, J=4.08Hz, 4.04Hz, 1H), 2.53~2.62 (m, 1H), 1.15~2.16 (m, 6H), 1.02 (t, J=7.4Hz, 3H), 1.03 (s, 3H), 0.91 (s, 3H), 0.90 (s, 3H). **2c** ^{1}H NMR δ ($CDCl_3$, 400MHz) 5.73~5.85 (m, 1H), 5.09~5.18 (m, 2H), 2.90~2.94 (m, 1H), 2.52~2.58 (m, 1H), 2.38~2.42 (m, 1H), 2.05 (d, J=13.8Hz, 1H), 1.84 (t, J=4.52Hz, 1H), 1.16~1.73 (m, 4H), 3.98 (dd, J=9.62Hz, 3.90Hz, 1H), 1.02 (s, 3H), 0.91 (s, 3H), 0.89 (s, 3H); $[\alpha]_D^{28}$ +75° (C=2, $CHCl_3$). **2d** ^{1}H NMR δ ($CDCl_3$, 400 MHz) 7.16~7.26 (m, 5H), 4.08 (dd, J=9.38Hz, 4.22Hz, 1H), 3.33 (dd, J=13.78Hz, 4.22Hz, 1H), 2.98 (dd, J=13.78Hz, 9.38Hz, 1H), 2.31~2.37 (m, 1H), 0.95 (s, 3H), 0.81 (s, 3H), 0.80 (s, 3H), 0.96~1.68 (m, 6H); $[\alpha]_D^{27}$ -18.5° (C=2, $CHCl_3$). **2d'** ^{1}H NMR δ ($CDCl_3$, 400MHz) 7.20~7.32 (m, 5H), 4.16 (dd, J=9.94Hz, 3.85Hz, 1H), 3.48 (dd, J=14.21Hz, 9.94Hz, 1H), 2.96 (dd, J=14.21Hz, 3.85Hz, 1H), 1.04~2.28 (m, 7H), 0.96 (s, 3H), 0.90 (s, 3H), 0.88 (s, 3H).

5. (a) Condensation of 8-phenylmenthone and glycolic acid gave an 1:1.3 selectivity. Pearson, W. H.; Cheng, M. C. *J. Org. Chem.* **1986**, *51*, 3746.
   (b) Condensation of *l*-menthone with t-butyl acetylacetate gave an 1:1 selectivity at 10°C, and 6:1 selectivity at -5°C (ca. 34% yield). Demuth, M.; Palomer, A.; Sluma, M.-D.; Dey, A. K.; Krüger, C.; Tsay, Y.-H. *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 1117.
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8. Optical rotation $[\alpha]_D^{30}$ -54° (C=1.8, $CHCl_3$). For a 92% optically pure (R)-ethyl *α*-methylthioglycolate, $[\alpha]_D^{22}$ +56.1° (C=2, $CHCl_3$).[3a]
9. Optical rotation $[\alpha]_D^{26}$ +59.6° (C=0.45, $CHCl_3$).

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