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Asymmetric synthesis employing chiral ketones as templates

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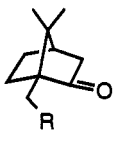
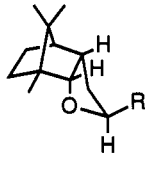
Abstract: Synthesis of optically active α-alkyl and α-arylthioglycolic acids from thioglycolic acid could be achieved by employing (1*R*)-(+)-camphor as the template. Asymmetric synthesis of D-daunosamine from thioglycolic acid through chiral 1,3-oxathiolan-5-one **5a** was achieved in six synthetic steps. Asymmetric synthesis of optically active 1,2-diols from alkynes through camphor derived chiral allenes is described. Preparation and synthetic application of chiral three carbon building blocks from glycerol could be achieved by employing (1*S*)-(+)-*N*,*N*-diisopropyl-10-camphorsulfonamide **2** as chiral template.

Synthesis of an enantiomerically pure biologically active molecule requires an enantiomerically pure starting material. They were normally obtained or derived from naturally occurring source.(ref. 1) It is a challenge for an organic chemist to devise a method to convert an achiral compound to a chiral compound by simple procedure through easy operations. We found that a chiral ketone with a rigid three-dimensional structure could provide an asymmetric environment for the enantioselective synthesis of organic molecules. Asymmetric synthesis employing (1*R*)-(+)-camphor **1** or (1*S*)-(+)-*N*,*N*-diisopropyl-10-camphorsulfonamide **2** as a chiral template in the syntheses of optically active molecules from prochiral compounds could be achieved with high enantioselectivity.



1 R = H
2 R = $SO_2N^iPr_2$



3 R = OCH_3
4 R = SCH_2COOH

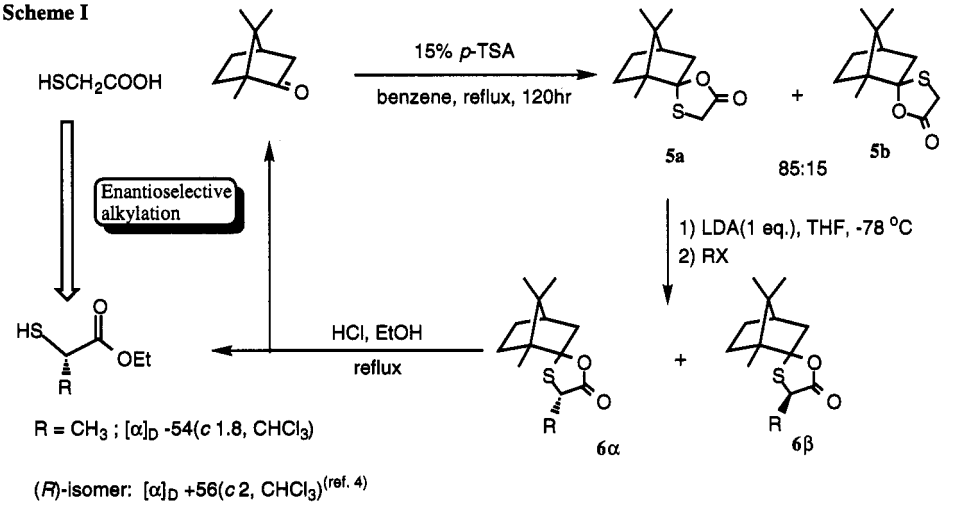
ASYMMETRIC SYNTHESIS FORM THIOGLYCOLIC ACID EMPLOYING (1*R*)-(+)-CAMPHOR AS THE TEMPLATE

The synthesis of optically active α-alkylthioglycolic acids has been reported by Noe where he employed acetal **3** as the chiral template.(ref. 2) In his report a large excess of base was used and the asymmetric induction on thioacetal **4** was at the level of 54% to 60% d.e. (diastereomeric enrichment). When 1,3-oxathiolan-5-one **5**, derived from the condensation of (1*R*)-(+)-camphor and thioglycolic acid, was treated with one equivalent of lithium diisopropylamide followed by alkyl halide, the major product was obtained as expected from the alkylation of the enolate on the less hindered α-face. The asymmetric induction could be achieved from 86% d.e. to > 98% d.e. (Table I). Ethanolysis of the major alkylation product in the presence of anhydrous hydrochloride gave optically active thioglycolate, with very little racemization, and recovered (1*R*)-(+)-camphor (Scheme I). (ref. 3)

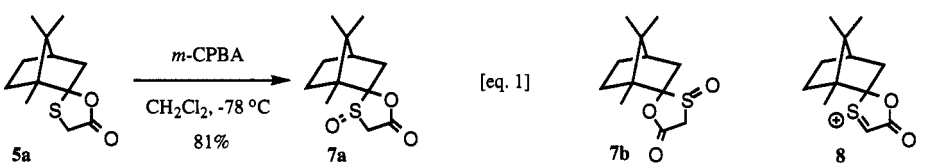
Table 1 Alkylation of the major 1,3-oxathiolan-5-one 5a

entry	RX	reaction condition	yield %	ratio 6α:6β (% d.e.)
1	CH_3I	-78 °C 20 min	>95	13:1(86)
2	C_2H_5I	-40 °C 30 min	70	13:1(86)
3	CH_2=CH-CH_2I	-78 °C 1 hr	89	104:1(98)
4	CH_2=CH-CH_2Br	-78 °C 1 hr	62	60:1(96.7)
5	CH_2=CH-CH_2Br	-40 °C 30 min	85	75:1(97.3)
6	$PhCH_2I$	-78 °C 1 hr	88	156:1(98.7)
7	$PhCH_2Br$	-78 °C 1 hr	71	98:1(98)

Scheme I



The optically active α-arylthioglycolic acids have been prepared from the corresponding optically active α-arylthioglycolic acids with inversion of configuration at α-carbon. (ref. 4) Preparation of α-aryl and α-heterosubstituted thioglycolic acids from **5** could be achieved by the oxidation of **5** with *m*-chloroperoxybenzoic acid to the corresponding *S*-oxide **7** followed by treatment with appropriate reagent. Reaction of **7a** with acetic anhydride in the presence of 5% *p*-toluenesulfonic acid at 20-25 °C gave **9**α and **9**β in a ratio of 20 to 1 (Scheme II). At higher reaction temperature the asymmetric induction was reduced (Table 2). The major product was formed from a nuclephilic attack of acetoxy anion from the less hindered α-face of the sulfenium ion intermediate **8**. When **7b** was reacted under a similar condition only a 4 to 1 ratio for the products was observed. Treatment of **7a** with trifluoroacetic anhydride in the presence of aromatic compound gave α-arylthioglycolic acid. Again, the major product was formed from an electrophilic aromatic substitution at the α-face of the sulfenium ion intermediate **8**. The asymmetric induction was observed from 78% d.e. to 100% d.e. (Table 3). Reaction using deactivated aromatic compounds, such as chlorobenzene, failed to give the desired product. (ref. 5)



Scheme II

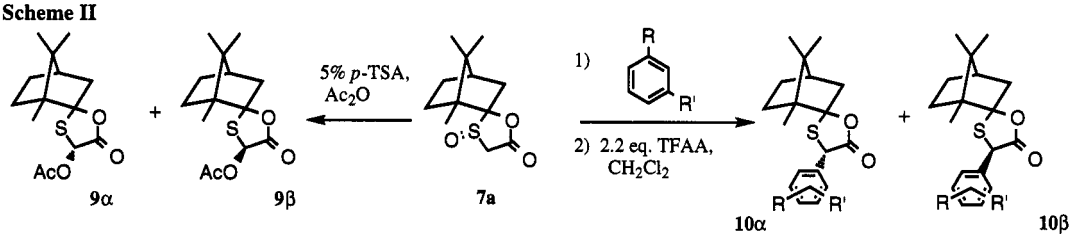


Table 2 Acetoxylation of 7a

entry	reaction condition	ratio α:β	yield %
1	CH_2Cl_2, 20-25 °C	20:1	79
2	$CHCl_3$, reflux	2.5:1	53
3	CH_2ClCH_2Cl, reflux	2.8:1	63

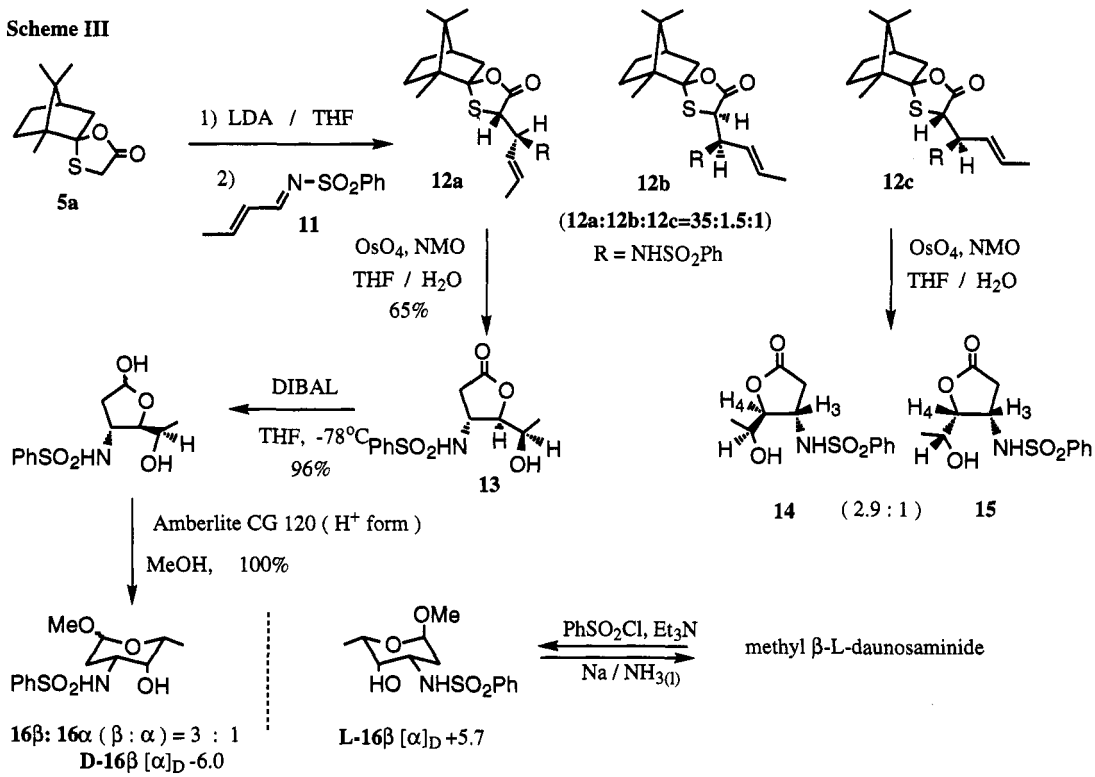
Table 3 Arylation of 7a

entry	R	R'	ratio α(*p*-:*o*-): β(*p*-:*o*-)	yield %
1	H	H	8.4:1	75
2	OCH_3	H	(16.4:8.4):(1.4:1)	79
3	CH_3	H	(13:2.6):(1:0)	75
4	OCH_3	OCH_3	100:0	63

Chiral 1,3-oxathiolanone **5** could serve as a chiral acetate equivalent in the synthesis of 3-amino-2,3,6-trideoxyhexopyranose. Chelation controlled condensation of **5a** with aldimine **11** gave one major aldol product **12a** in high diastereoselectivity (Scheme III). Dihydroxylation of **12a** with OsO_4/NMO gave

one δ-hydroxy-γ-butyrolactone **13** in 65% yield, whereas **12c**, an epimer of **12a**, gave lactones **14** and **15** as the products in 2.9 to 1 ratio. Lactones **13** and **14** have identical spectral data and similar magnitude in optical rotation except that they were opposite in sign. Lactone **13** was converted to D-daunosamine in two steps.(ref. 6)

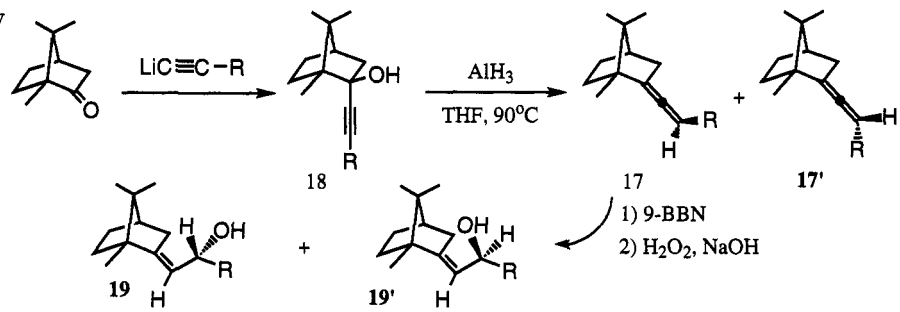
Scheme III



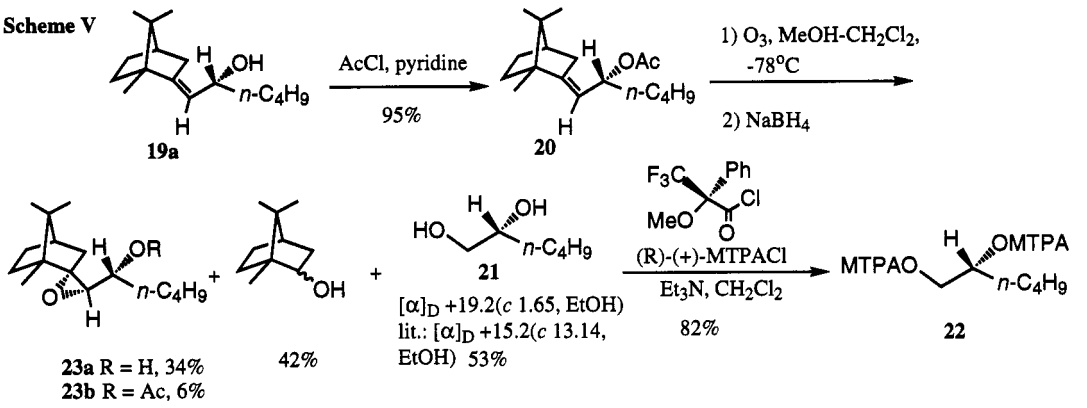
ASYMMETRIC SYNTHESIS OF 1,2-DIOL VIA CHIRAL ALLENE EMPLOYING (1*R*)-(+)-CAMPHOR AS THE TEMPLATE

There are many reports dealing with the asymmetric synthesis through chiral allenes, derived from optically active precursors, as the key intermediates.(ref. 7) However there is no report of any sucessful asymmetric synthesis from an achiral precursor through chiral allenes. Chiral allenes **17** could be prepared from (1*R*)-(+)-camphor and alkynes through chiral propargyl alcohols **18** (Scheme IV).(ref. 8) Reaction of chiral allene **17** with 9-BBN followed by oxidative workup gave allylic alcohols **19** in high diastereoselectivity (Table 4). The formation of alcohol **19** presumably arose from the addition of 9-BBN from the less hindered face followed by an allylborane rearrangement.(ref. 9) Alcohol **19a** could be converted into (*R*)-1,2-diol **21** in good yield by acetylation of the hydroxy group to acetate **20** followed by ozonolysis with reductive workup (Scheme V). Bis-Mosher ester **22** is enantiomerically pure.

Scheme IV



Scheme V



19a **20** **21** **22**

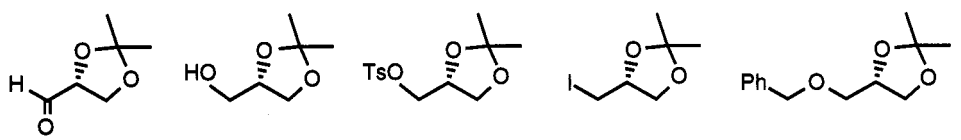
23a R = H, 34%
23b R = Ac, 6%

Table 4 Asymmetric hydroboration/oxidation of 17

	R	19:19'	yield(%)
17a	*n*-C_4H_9	15:1	82
17b	CH_3	6:1	66
17c	*n*-C_3H_7	15:1	80
17d	*n*-C_5H_{11}	17:1	77
17e	CH_2CH_2OBn	15:1	76

ASYMMETRIC SYNTHESIS FROM GLYCEROL EMPLOYING (1*S*)-(+)-*N*,*N*-DIISOPROPYL-10-CAMPHORSULFONAMIDE AS THE TEMPLATE

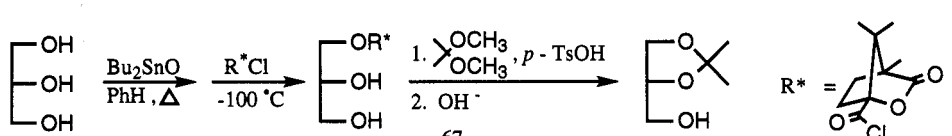
Chiral glyceraldehyde **24,** glycerol **25**, and its derivatives, such as tosylate **26**, iodide **27**, or benzyl ether **28** are important three carbon chiral building blocks for the synthesis of enantiomerically pure biologically active molecules.(ref. 10) Traditionally this series of compounds, (*S*)-**24** and (*R*)-**25**, were prepared from D-mannitol.(ref. 11) Chiral glycerol **25** and its derivatives **26-28** were then obtained by the reduction of **24**, and further manipulation on the free hydroxyl group of **25**. This series of compounds with opposite configuration were obtained from L-serine or ascorbic acid via a few chemical operations.(ref. 12) These procedures require the use of lead tetraacetate, which is usually difficult to handle on a large scale operation.



24 **25** **26** **27** **28**

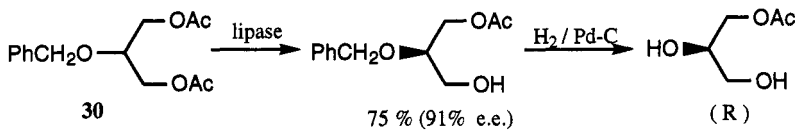
Glycerol, relatively, is an inexpensive material. However, glycerol itself has never been seriously considered as an alternative source of chiral building blocks until 1984. In principle, chiral glycerol derivatives could be prepared from glycerol by the differentiation of the two enantiotopic prochiral hydroxymethyl groups and the transformation of one of the hydroxyl group to a desired functionality. The kinetic resolution method was explored by Mukaiyama and coworkers. They found that treatment of glycerol with dibutyltin oxide followed by (-)-camphanic acid chloride **29** would give two diastereomeric isomers in 95 to 5 ratio (Scheme V). (ref. 13) However, it required four moles excess of dibutyltin ester, prepared from the reaction of glycerol and dibutyltin oxide, for this reaction to obtain best result. Two years later, Schneider and coworkers reported a method using lipase catalyzed hydrolysis reaction to differentiate the two prochiral acetoxymethyl groups of glycerol derivative **30** in 91% e.e. (SchemeVII).(ref. 14)

Scheme VI



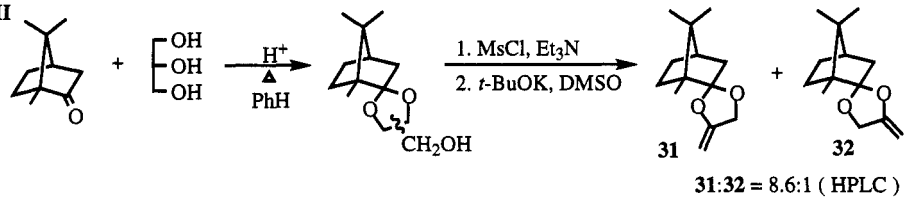
5 mole excess 78% (90% d.e.) **29**

Scheme VII

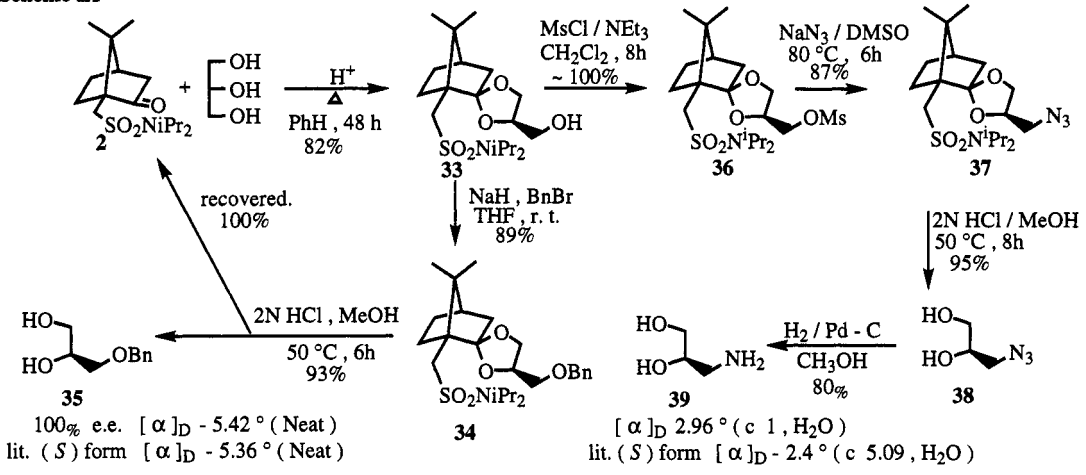


When a benzene solution containing camphor, glycerol, and a catalytic amount of *p*-toluenesulfonic acid was heated under reflux for 4.5 days with removal of water, a mixture of four diastereomers was obtained as judged by the HPLC analysis of this mixture. These four isomers were treated with methanesulfonyl chloride in the presence of triethylamine in dichloromethane followed by treatment with potassium *t*-butoxide in dimethylsulfoxide to give two olefinic compounds **31** and **32** in a ratio of 8.6 to 1 (Scheme VIII).(ref. 15) Surprisingly, when a benzene solution containing (1*S*)-(+)-*N*,*N*-diisopropyl-10-camphorsulfonamide **2**, glycerol, and a catalytic amount of *p*-toluenesulfonic acid was heated under reflux for 36 hours with removal of water, the major acetal **33** was obtained by silica gel column chromatography in 82% yield. The formation of the major acetal **33** presumably arose from the attack of the pro-*R* primary alcohol of glycerol to the carbonyl group from the endo position of **2** followed by a cyclization with the secondary alcohol of glycerol from the endo position, the reaction being driven by hydrogen bonding between the free OH and the sulfonamido groups. Treatment of **33** with sodium hydride in tetrahydrofuran followed by benzyl bromide gave benzyl ether **34** in 89% yield. Hydrolysis of benzyl ether **34** in methanol with 2 N hydrochloric acid afforded (*S*)-1-benzyloxy-2,3-propanediol **35** in 93 % yield and completely recovered **2** (Scheme IX).(ref. 16) On the other hand, treatment of **33** with methanesulfonyl chloride and triethylamine in dichloromethane for 8 hours afforded the corresponding mesylate **36.** Reaction of crude **36** with sodium azide in dimethylsulfoxide gave azide **37** in 87% yield. Hydrolysis of **37** in methanol with 2N hydrochloric acid liberated azidodiol **38** in 95% yield and recovered **2** in nearly quantitative yield. Hydrogenation of azidodiol **38** in methanol with 10% Pd/C afforded (*R*)-1-amino-2,3-propanediol **39** in 80% yield (Scheme IX). (ref. 16)

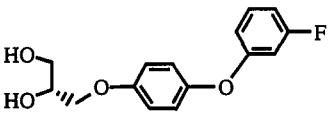
Scheme VIII



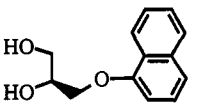
Scheme IX



Preparation of **40** as key intermediate for the synthesis of insect regulator from *ent*-**36** has been reported employing this strategy, in 63% yield, with >98% enantiomeric purity. (ref. 17) Treatment of mesylate **36** with α-naphthol in the presence of potassium carbonate in DMSO followed by methanolysis gave **41**, a precursor for the synthesis of (*S*)-propranolol, in 61% yield. (ref. 18, 19)



40



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In conclusion, chiral ketones with rigid three dimensional structure are good templates for the asymmetric synthesis of optically active molecules from a prochiral precursor.

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