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Versatile Chiral Synthons for *vic*-Amino Alcohols. Facile Synthesis of (2*S*,3*R*)-3-Hydroxyglutamic Acid and (+)-Statine

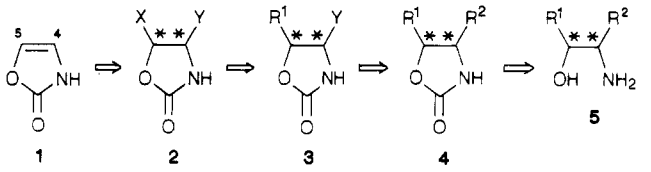
Summary: Functionalization of the 3-ketopinyl-2-oxazolone ring with a new reagent system, $Br_2/CH_3C(OCH_3)_3$/TMSOTf, results in highly diastereoselective formation of 5-bromo-4-methoxy-2-oxazolidinone derivatives **2**, which serve well as versatile chiral synthons for biologically significant *vic*-amino hydroxy compounds.

Sir: Our continuing work on the synthetic utility of the 2-oxazolone heterocycle has revealed its synthetic potential as an excellent leaving group in carboxy[1] and phosphoryl[2] activating processes. Such a leaving ability has led to the development of excellent condensing reagents for the formation of peptides,[1] β-lactams,[3] thio esters[4] and mixed phosphates.[2]

This paper describes another synthetic application of the simple heterocycle **1** as a building block for *vic*-amino alcohol structures, which are structural units found in a number of bioactive compounds such as amino sugar antibiotics, enzyme peptidic inhibitors and sympathomimetic amines.[5] The synthetic strategy shown in Scheme I offers versatile routes to a wide variety of *vic*-amino alcohols, in which the key step is functionalization of the olefinic moiety of the 2-oxazolone ring by regio- and stereodefined introductions of easily replaceable groups (X and Y), followed by stereospecific and stepwise substitutions with appropriate groups (R^1 and R^2). This methodology would be expected to result in predominant formation of threo derivatives, which could be readily converted to erythro configuration by inversion of the hydroxy group via oxazoline intermediates.[6a] This may be the most reliable and convenient route which can avoid serious side reactions such as β-elimination and epimerization, as evidenced by the mutual transformation of threonine and *allo*-threonine.[6b]

Bromo and methoxy groups were chosen as suitable functionalities for X and Y in compounds **2**, which have acetal-like structures sensitive to both nucleophilic and

Scheme I



Scheme II

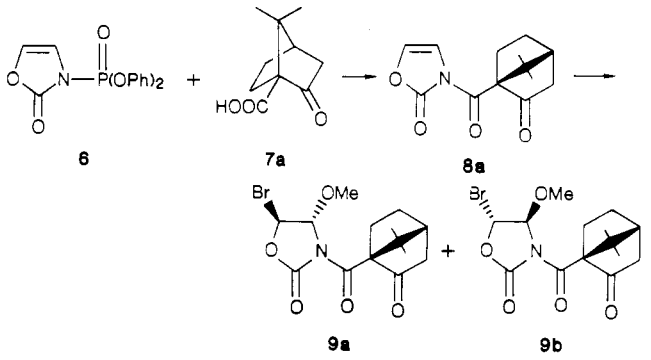


Table I. Diastereoselective Functionalization of (−)-3-Ketopinyl-2-oxazolone (8a)[a]

entry	conditions	yield,[b] %	ratio[c] 9a:9b
1	NBS, MeOH–dioxane, 20 °C	68 (0)	63:37
2	NBS, MeOH, −70 °C	54 (6)	57:43
3	Br_2, MeOH, 0 °C	47 (5)	68:32
4	Br_2, MeOH, −70 °C	75 (13)	81:19
5	Br_2, $MeC(OMe)_3$, −70 °C	58 (8)	90:10
6	Br_2, $MeC(OMe)_3$, TMSOTf, −70 °C	76 (10)	92:8
7	Br_2, $MeC(OMe)_3$, $ZnBr_2$, −70 °C	76 (11)	90:10
8	Br_2, $HC(OMe)_3$, TMSOTf, −70 °C	63 (6)	85:15
9	Br_2, $MeSi(OMe)_3$, TMSOTf, −70 °C	70 (14)	82:18
10	Br_2, $MeC(OMe)_3$, TMSOTf, −100 °C	78 (5)	95:5

[a] All reactions were run under the conditions given for 30 min (see text). [b] In isolated pure compounds. The numbers in parentheses refer to the yield of the 4,5-dibromo adducts. [c] Determined by ^1H NMR (400 MHz) analysis.[11]

radical species. The chiral synthons **2** are obtained in a diastereoselective manner from optically active 3-acyl-2-oxazolones, which are readily available on treatment of diphenyl (2-oxo-3-oxazolinyl)phosphonate (DPPOx)[1] (**6**) with a wide variety of chiral carboxylic acids. Among the chiral auxiliaries examined, including α-amino acid derivatives, (+)- and (−)-ketopinic acids (2-oxo-7,7-dimethylbicyclo[2.2.1]heptane-1-carboxylic acids)[7] (**7a** and **7b**) (Scheme II) were found to be the best choice owing to the availability of both enantiomers, the high diastereoselectivity attained, and the ease of separation of the diastereoisomers.

Thus, treatment of (−)-3-ketopinyl-2-oxazolone (**8a**) (mp 129 °C, $[\alpha]^{20}_D$ −49.2° ($CHCl_3$)) derived from (+)-ketopinic acid (**7a**) with *N*-bromosuccinimide (NBS) or bromine in methanol resulted in highly regioselective formation of *trans*-5-bromo-4-methoxy-2-oxazolidinone adducts (**9a** and **9b**) in rather low diastereoselectivity (up to 62% de).[8] On

(1) Kunieda, T.; Higuchi, T.; Abe, Y.; Hirobe, M. *Tetrahedron* **1983**, *39*, 3253.
(2) Nagamatsu, T.; Kunieda, T. *Tetrahedron Lett.* **1987**, *28*, 2375.
(3) Kunieda, T.; Nagamatsu, T.; Higuchi, T.; Hirobe, M. *Tetrahedron Lett.*, in press.
(4) Kunieda, T.; Abe, Y.; Hirobe, M. *Chem. Lett.* **1984**, 1465.
(5) For examples, see: (a) Hata, T.; Omura, S.; Katagiri, M.; Atsumi, K.; Awaya, J.; Yasui, K.; Terada, H.; Kuyama, S. *J. Antibiot.* **1971**, *24*, 900. (b) Umezawa, H.; Aoyagi, T.; Suda, H.; Hamada, M.; Takeuchi, T. *J. Antibiot.* **1976**, *29*, 97. (c) Dukes, M.; Smith, L. *J. Med. Chem.* **1971**, *14*, 326.
(6) (a) Fry, E. M. *J. Org. Chem.* **1949**, *14*, 887. (b) Treatment of *N*-benzoyl-L-threonine methyl ester with thionyl chloride in ether followed by acidic hydrolysis gave L-*allo*-threonine in 67% yield without any detectable threo configurations. Similarly *N*-benzoyl-L-*allo*-threonine gave back optically pure L-threonine in 83% yield.
(7) The acids **7a,b** were readily prepared in 40% yields by permanganate oxidation of commercially available (1*S*)- and (1*R*)-10-camphorsulfonic acids, according to the literature method: Bartlett, P. D.; Knox, L. H. *Org. Synth.* **1965**, *45*, 14, 55.
(8) Conventional reagent systems for functionalization of alkenes such as NBS/AcOH, PhSeCl/MeOH, and PhSeBr/MeOH similarly reacted with compounds **8a,b** to give good yields of regioselective adducts, but the diastereoselectivity never exceeded 50% de under a wide scope of conditions. We thank F. Ogata of Kumamoto University for her skillful technical assistance in this part of studies.

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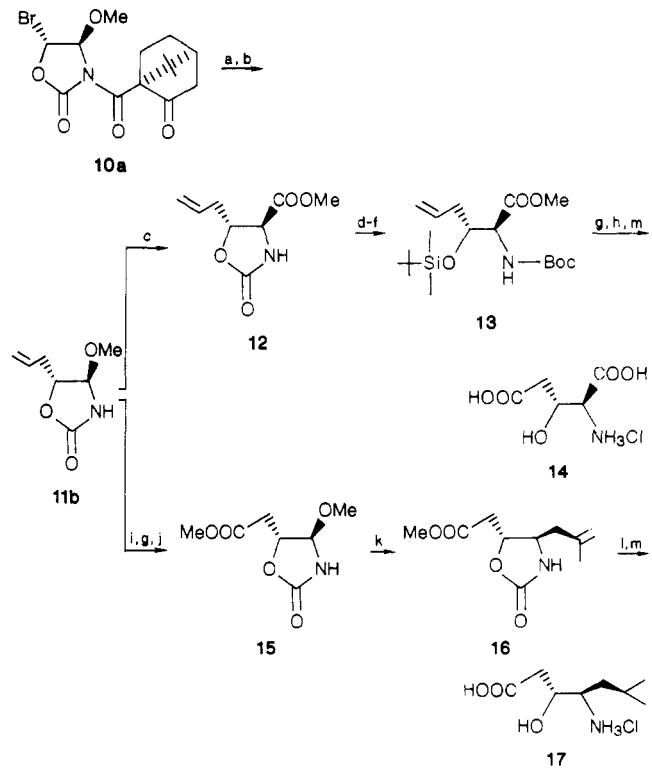
the other hand, the diastereoselectivity was greatly improved (up to 90% de) when compound **8a** was treated with bromine in a large excess of trimethyl orthoesters using Lewis acids as activators (Table I). Among methylal and trimethyl orthoformate, orthoacetate, and orthobenzoate, and trimethoxymethylsilane examined as methoxy-donating agents, the orthoacetate gave the best results with regard to selectivity and yield of the 5-bromo-4-methoxy adducts **9a,b**. Trimethylsilyl triflate (TMSOTf) was the activator of choice among the Lewis acids examined.[9] This reagent system has good generality for functionalization of a wide variety of alkenes under neutral conditions.[10]

A typical experimental procedure was as follows. A solution of bromine (1.4 mmol) in dichloromethane (5 mL) was added dropwise over 30 min to a mixture of (−)-3-ketopinyl-2-oxazolone (**8a**) (1 mmol), trimethyl orthoacetate (5 mL), and TMSOTf (1 mmol) at −100 °C. After complete addition, the mixture was quickly passed through a short column of silica gel with dichloromethane as the eluent to remove the triflate and the eluate was evaporated in vacuo. The ^{1}H NMR spectrum of the residue showed a diastereomeric ratio (**9a:9b**) of 95:5[11] in addition to the 4,5-dibromo adduct in 5% yield. Chromatography on silica gel with dichloromethane gave 74% and 4% yields of (4*S*,5*S*)- and (4*R*,5*R*)-5-bromo-4-methoxy-2-oxazolidinone derivatives (**9a** and **9b**),[11] respectively.

The (4*R*,5*R*)-5-bromo-4-methoxy adduct **10a** (mp 171 °C, $[\alpha]^{19}_D$ +88° ($CHCl_3$)), the antipode of **9a**, was analogously obtained as a major isomer in optically pure form by single recrystallization of the products arising from (+)-3-ketopinyl-2-oxazolone (**8b**) (mp 130 °C, $[\alpha]^{20}_D$ +48.3° ($CHCl_3$)). The absolute configurations of these adducts were inferred by chemical correlation of **10a** with (3*R*)-4-amino-3-hydroxybutyric acid (GABOB) of known configuration[12] and further supported by transformation to the known compounds as described in Scheme III.

Enantiomers **9a** and **10a** thus obtained were successfully utilized as common synthons for chiral synthesis of some *vic*-amino alcohols of biological interest, according to the synthetic routes outlined in Scheme III. Treatment of the adducts **9a** and **10a** with allyltributyltin under UV irradiation, followed by deacylation with dibutylcuprate, gave 68-71% yields of the (4*S*,5*S*)- and (4*R*,5*R*)-5-allyl-4-methoxy-2-oxazolidones (**11a** and **11b**), respectively, with full retention of configuration;[13] the versatility of these

Scheme III[a]



[a] (a) $\sim$SnBu$_3$/*hν* (85%); (b) Bu_2CuLi (83%); (c) (1) TMSCN/$TiCl_4$, (2) MeOH/HCl (62%); (d) $(Boc)_2O$/NaH (87%); (e) Cs_2CO_3/MeOH (86%); (f) TBDMSiCl/imidazole (82%); (g) (1) $KMnO_4$–$NaIO_4$, (2) CH_2N_2 (85%); (h) TBAF/0 °C (79%); (i) AcCl/BuLi (72%); (j) $SnCl_2$–Mg/MeOH (71%); (k) $\swarrow$SnBu$_3$/$SnCl_4$ (75%); (l) H_2/Pd–C (95%); (m) 6 N HCl (100 °C) (92%).

enantiomers was demonstrated by oxidative cleavage of the allyl group to a carboxymethyl moiety and stereospecific displacements of the 4-methoxy group with cyano and methallyl groups.[14] Thus, (2*S*,3*R*)-3-hydroxyglutamic acid (**14**)[15] and (3*R*,4*R*)-4-amino-3-hydroxy-6-methylheptanoic acid ((+)-statine) (**17**)[16] were conveniently obtained as the hydrochlorides from **10a** and the characterizations were performed in protected forms. It is noteworthy that ring-opening of the 2-oxazolidinone (**12** → **13**) with catalytic amounts of cesium carbonate or bicarbonate in

(9) The following Lewis acids were examined: $ZnCl_2$, $ZnBr_2$, $ZrCl_4$, $SnCl_2$, $AlBr_3$, Ti(O-*i*-Pr)$_4$, and $TiCl_4$.

(10) The system smoothly reacted with a wide variety of alkenes including vinyl ethers and enamines to give the corresponding bromo methoxy adducts, whose synthetic utilities will be reported in due course.

(11) The ratio was based on the relative intensities of the NMR signals distinctly resolved at δ 5.77 and 5.86. **9a**: mp 167 °C; $[\alpha]^{21}_D$ −90° ($CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.19 (s, 1 H), 5.77 (s, 1 H), 3.55 (s, 3 H), 3.09–3.02 (m, 1 H), 2.51–2.44 (m, 1 H), 2.24–1.97 (m, 4 H), 1.58-1.52 (m, 1 H), 1.28 (s, 3 H), 1.14 (s, 3H). **9b**: mp 130 °C; $[\alpha]^{20}_D$ +116° ($CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.22 (s, 1 H), 5.86 (s, 1 H), 3.52 (s, 3 H), 2.86–2.80 (m, 1 H), 2.52–2.44 (m, 1 H), 2.24–1.97 (m, 4 H), 1.58–1.52 (m, 1 H), 1.28 (s, 3 H), 1.14 (s, 3 H).

(12) (a) Compound **11b** derived from **10a** (see text) was converted to methyl (3*R*)-*N*-*t*-Boc-4-amino-3-hydroxybutyrate ($[\alpha]^{20}_D$ +5.4° ($CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.07 (br, 1 H), 4.1 (m, 1 H), 3.71 (s, 3 H), 3.35 (br, 1 H), 3.12 (m, 2 H), 2.50 (m, 2 H), 1.45 (s, 9 H)), whose purity was shown above 99% ee by the Mosher's method.[18] The 3*R* stereochemistry of this amino acid was determined by the conversion to 4-benzamido-3-hydroxybutyric acid, $[\alpha]^{21}_D$ −9.8° (H_2O) (lit. $[\alpha]_D$ −11.8° (H_2O) for the *R* isomer;[12b] $[\alpha]_D$ +10.0° (H_2O) for the *S* isomer[12c]). (b) Kaneko, T.; Yoshida, R. *Bull. Chem. Soc. Jpn.* **1962**, *35*, 1153. (c) Tomita, M.; Sendju, Y. *Hoppe-Seyler's Physiol. Chem.* **1927**, *169*, 266.

(13) Compounds **11a** (mp 50.5 °C, $[\alpha]^{20}_D$ −114.6° ($CHCl_3$)) and **11b** ($[\alpha]^{20}_D$ +114.5° ($CHCl_3$)) are enantiomeric, and the trans stereochemistry was shown by ^{1}H NMR analysis: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (br, 1 H), 5.70–5.84 (m, 1 H), 4.70 (d, 1 H, *J* = 2 Hz), 4.45 (dt, 1 H, *J* = 2, 6 Hz), 3.33 (s, 3 H), 2.38–2.58 (m, 2 H).

(14) Facile inversion of the hydroxy stereochemistry via oxazoline intermediates[6] would be helpful since the manipulation on the trans adducts returned the trans stereochemistry in the resulting product. Thus, *threo*-3-hydroxyglutamic acid was converted to the erythro compound in 70% yield.[15]

(15) Shoji, J.; Sakazaki, R. *J. Antibiot.* **1970**, *23*, 418. This hydrochloride, mp 203 °C (lit.[17] mp 201 °C), was fully characterized as the *N*-*t*-Boc dimethyl ester; $[\alpha]^{20}_D$ +28.9° ($CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.42 (d, 1 H, *J* = 9.5 Hz), 4.60 (br, 1 H), 4.35 (br d, 1 H, *J* = 9.5 Hz), 3.78 (s, 3 H), 3.72 (s, 3 H), 3.47 (d, 1 H, *J* = 4.4 Hz), 2.68–2.53 (m, 2 H), 1.45 (s, 9 H) (the 2*S*,3*S*-erythro isomer:[14] $[\alpha]^{20}_D$ +21.4° ($CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.3 (br, 1 H), 4.26–4.44 (m, 2 H), 3.78 (s, 3 H), 3.71 (s, 3 H), 2.69 (dd, 1 H, *J* = 8.79, 16.5 Hz), 2.62 (dd, 1 H, *j* = 3.66, 16.5 Hz). Optical purity was shown at least 99% ee by the Mosher's method.[18]

(16) Umezawa, H.; Aoyagi, T.; Morishima, H.; Matsuzaki, M.; Hamada, H.; Takeuchi, T. *J. Antibiot.* **1970**, *23*, 259. (+)-Statine hydrochloride (**17**) was characterized as the *N*-*t*-Boc ethyl ester: $[\alpha]^{20}_D$ +34.5° (MeOH) (lit.[19] $[\alpha]^{20}_D$ −37.9° (MeOH) for the 3*S*,4*S* isomer); ^{1}H NMR (100 MHz, $CDCl_3$) δ 5.6 (br, 1 H), 4.4–3.95 (m, 1 H), 4.19 (q, 2 H, *J* = 6.5 Hz), 3.7–3.4 (m, 1 H), 2.8–2.45 (m, 2 H), 1.8–1.5 (m, 3 H), 1.45 (s, 9 H), 1.29 (t, 3 H, *J* = 6.5 Hz), 0.92 (d, 6 H, *J* = 6.0 Hz).

(17) Kaneko, T.; Yoshida, Y.; Katsura, H. *Nippon Kagaku Zasshi* **1959**, *80*, 316.

(18) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543.

(19) Rich, D. H.; Sun, E. T.; Boparai, A. S. *J. Org. Chem.* **1978**, *43*, 3624.

methanol was mild and selective enough to leave the ester and *tert*-butoxycarbonyl groups unaffected.[20]

In conclusion, great versatility of the chiral synthons of type **2** should result from the smooth and stepwise displacements of substituents at the 4- and 5-positions of oxazolidinone heterocycles, as described here for a few examples.[21] Applications of the present methodology to the facile preparation of amino sugars and peptides of biological interest are now under investigation.

Supplementary Material Available: Experimental and spectral data for compounds **11b–13** and **11b–16** (3 pages). Ordering information is given on any current masthead page.

(20) Ishizuka, T.; Kunieda, T. *Tetrahedron Lett.* **1987**, *28*, 4185.
(21) Typical functions other than groups presented here as R^1 and R^2 include cyano, cyanoethyl, carboxyethyl, and vinyl groups at 5-position and allyl, aryl, and acetonyl groups at 4-position. Ishizuka, T.; Ishihara, H.; Oosaki, M.; Kunieda, T.; Higuchi, T.; Hirobe, M. *The 18th Congress of Heterocyclic Chemistry*; Fukuoka: Japan, 1986; Abstract p 289.

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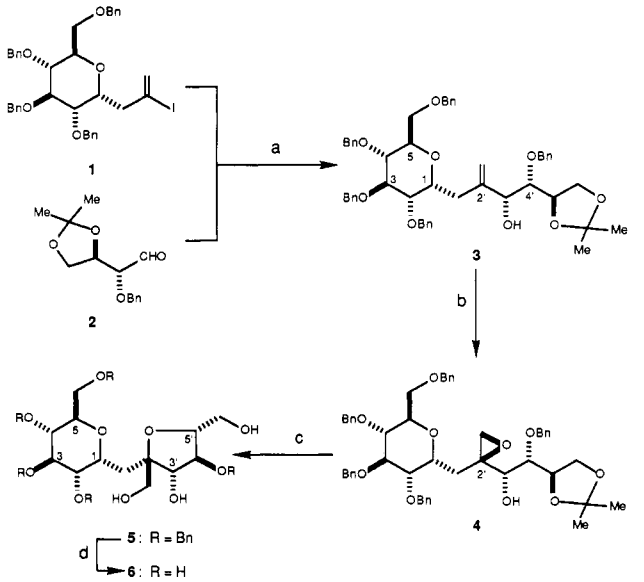
Synthesis of C-Sucrose

Summary: C-Sucrose has been synthesized in six steps from vinyl iodide **1** and aldehyde **2** with approximately 30% overall yield. The synthetic route developed is flexible enough to prepare C2′ and C3′ stereoisomers of C-sucrose and related compounds.

Sir: We have recently reported results of studies which examined the conformational preferences of certain C-disaccharides and showed that they could be favorably compared to their oxygen counterparts.[1] Our attention has now turned to other biologically important saccharides. One such project is to examine the conformational preference of C-sucrose and to study its effect on the sweetness receptor. The information gained from these studies would provide a valuable insight about the structure of the receptor, and could facilitate the rational design of nonnutritive sweeteners.[2] In this paper we wish to report the synthesis of C-sucrose.

The success of the synthesis depended on two key reactions (Scheme I). The first of these exploits the recently developed Ni(II)/Cr(II)-mediated coupling of vinyl iodides to aldehydes.[3] This reaction would provide a mild and convenient procedure for construction of the required carbon backbone from vinyl iodide **1** and aldehyde **2**. It was envisaged that the other key reaction, formation of the fructose ring of **5**, would involve acid-catalyzed ring-

Scheme I[a]



[a] Reagents and reaction conditions: (a) (1) $NiCl_2$ (0.1%)–$CrCl_2$/THF–DMSO (4:1)/room temperature; (2) $(EtO_2CN{=})_2$/P-$(Ph)_3$/$PhCO_2H$/PhH/room temperature; (3) K_2CO_3/MeOH/room temperature; (b) MCPBA/CH_2Cl_2/room temperature; (c) CSA/wet CH_2Cl_2 (saturated)/room temperature; (d) H_2 (1 atm)/10% $Pd(OH)_2$ on C/MeOH/room temperature.

opening of the epoxide **4** and concomitant cyclization by intramolecular attack of the secondary hydroxyl functionality.

The required fragments for the coupling reaction were readily available. Vinyl iodide **1** was synthesized from the corresponding vinyl bromide[4] in one step.[5] Aldehyde **2**[6] was synthesized from 2,3-*O*-dibenzyl-4,5-*O*-isopropylidene-D-arabinose[7] in three steps.[8] The unstable aldehyde **2** was used immediately in the coupling reaction with **1** to produce an approximately 10:1 mixture of the expected allylic alcohols.[9] The stereochemistry of the major product was tentatively assigned as erythro, based on previous examples of Ni(II)/Cr(II)-mediated couplings.[3a] Since the desired threo alcohol **3** was the minor product of the coupling, attempts were made to invert the stereochemistry at C3′. Among several possibilities examined a modified Mitsunobu procedure[10] gave the most satisfactory results.[11]

By utilizing the directing effect of the free allylic hydroxyl group, *m*-chloroperbenzoic acid (MCPBA) epoxidation[12] of the threo allylic alcohol **3** gave a 1:3 mixture of syn and anti epoxy alcohols in 94% yield. Conversely, the Ti(*i*-OPr)$_4$/*t*-BuO_2H epoxidation[13] yielded a 12:1 mixture of syn and anti epoxy alcohols in 72% yield. The

(1) (a) Wu, T.-C.; Goekjian, P. G.; Kishi, Y. *J. Org. Chem.* **1987**, *52*, 4819. (b) Goekjian, P. G.; Wu, T.-C.; Kang, H.-Y.; Kishi, Y. *J. Org. Chem.* **1987**, *52*, 4823. (c) Babirad, S. A.; Wang, Y.; Goekjian, P. G.; Kishi, Y. *J. Org. Chem.* **1987**, *52*, 4825.
(2) For a review of nonnutritive sweeteners, see: DuBois, G. E. *Annu. Rep. Med. Chem.* **1982**, *17*, 323.
(3) (a) Jin, H.; Uenishi, J.; Christ, W. J.; Kishi, Y. *J. Am. Chem. Soc.* **1986**, *108*, 5644. (b) Takai, K.; Tagashira, M.; Kuroda, T.; Oshima, K.; Utimoto, K.; Nozaki, H. *J. Am. Chem. Soc.* **1986**, *108*, 6048.
(4) Hosami, A.; Sakata, Y.; Sakurai, H. *Tetrahedron Lett* **1984**, *25*, 2383.
(5) The vinyl bromide was treated with *t*-BuLi/THF/−78 °C, followed by iodine quench at −78 °C.
(6) For a synthesis of the antipode, see: Williams, D. R.; Klingler, F. D. *Tetrahedron Lett.* **1987**, *28*, 869.
(7) Babirad, S. A.; Wang, Y.; Kishi, Y. *J. Org. Chem.* **1987**, *52*, 1370.
(8) These three steps are: (a) MCPBA/CH_2Cl_2/phosphate buffer (pH 7)/room temperature. (b) $LiAlH_4$/Et_2O/0 °C. (c) Swern oxidation.
(9) The ratio was based on the isolated products.
(10) For a review on this subject, see: Mitsunobu, O. *Synthesis* **1981**, 1.
(11) Significant scrambling of the C3′ position occured when THF was employed as solvent, probably via the intermediacy of an allylic cation.
(12) Johnson, M. R.; Kishi, Y. *Tetrahedron Lett.* **1979**, 4347 and references cited therein.
(13) Isobe, M.; Kitamura, M.; Mio, S.; Goto, T. *Tetrahedron Lett* **1982**, *23*, 221 and references cited therein. MCPBA epoxidation of the triethylsilyl derivative of **3** yielded a 2:1 mixture of syn and anti epoxides.

0022-3263/88/1953-3383$01.50/0