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# Zirconocene-Catalyzed Epoxy Ester - Ortho Ester Rearrangement: A New Method for the Protection of Polyfunctionalized Carboxylic Acids and the Asymmetric Synthesis of Ortho Esters

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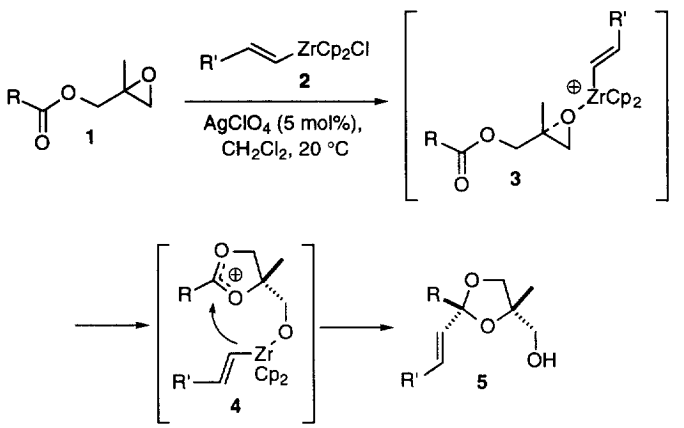
**Abstract:** *In situ* prepared $Cp_2(Cl)Zr^{\oplus}$ catalyzes the formation of ortho esters from epoxy esters. Acid-sensitive α-amino and α-hydroxy acid derivatives are converted in high yield to 2,7,8-trioxabicyclo[3.2.1]octanes (ABO-esters) using this protocol. This strategy is complementary to the OBO-ester technology, and orthogonal methods for the deprotection of ABO- and OBO-esters have been developed. The syntheses of the mushroom components (*S*)-γ-hydroxyleucine lactone and (*S*)-α-vinylglycine underline the value of ABO-ester protective group strategy. Using chiral epoxy alcohol derivatives, the first convenient and general asymmetric synthesis of bicyclic ortho esters has been achieved. © 1997 Elsevier Science Ltd.

## Introduction

Neutral d(0)-metallocenes of the general formula $Cp_2MX_2$ (M = Ti, Zr, Hf; X = Cl, Br, I) represent the most extensively studied class of group IVB organometallic compounds.[1] Since the mid-1970's, considerable interest in these complexes has been nurtured by the development of many applications of Schwartz reagent ($Cp_2ZrHCl$) in synthetic organic chemistry.[2] Insertion and transmetalation reactions of organozirconocenes have been extensively investigated and utilized in synthesis. The chemistry of the related 14-electron $Cp_2(R)M^+$ complexes (M = Ti, Zr) has been developed since the mid 1980's.[3] Their greater reactivity can be attributed to the significantly increased Lewis acidity of the metal center. This promotes coordination and activation of various Lewis basic substrates and opens reaction pathways that are unavailable to the neutral 16-electron complexes.[2a,4]

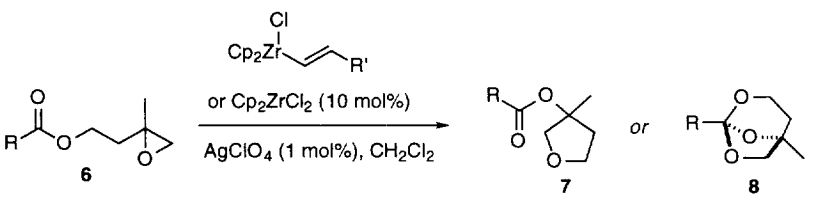
In prior studies, we have found that the cationic zirconocene species prepared *in situ* from organozirconocene and catalytic amounts of $AgClO_4$ are efficient in initiating tandem epoxide rearrangement-aldehyde addition cascades[5] and are compatible with a wide range of functional groups in the formation of dioxolanes from epoxy esters.[6,7,8] In the latter reactions, it is likely that dioxolenium ions **4** are formed as intermediate species preceding C,C-bond formation (Scheme 1).

**Scheme 1**




Interestingly, chain extension of the epoxyester substrate from **1** to **6** provided acyloxytetrahydrofurans **7** and orthoesters **8** depending on the nature of the substituent R (Scheme 2).[6] No transfer of the organic ligand on the zirconocene to the epoxyester substrate was noted in this reaction, and, accordingly, a catalytic protocol using 5-15 mol% of commercially available zirconocene dichloride and 1-2 mol% of $AgClO_4$ could be used instead. In this paper, we report on the scope of this new catalytic method for ortho ester synthesis.

**Scheme 2**




## Results and Discussion

Treatment of a solution of succinate **9** and 0.1 equiv of zirconocene dichloride in $CH_2Cl_2$ with 0.01 equiv of silver(I) perchlorate[9] (1 mol%) at room temperature for 15 min provided the orthoester **10** in 96% yield (Scheme 3). Similarly, the chloro ester **11** was converted in 93% yield without interference by the halogen substituent in the presence of 0.01 equiv of silver(I) salt. Product formation can be explained by irreversible formation of the cationic zirconocene **14**, followed by neighboring-group assisted Lewis-acid induced opening of the epoxide to give the dialkoxycarbenium ion **16** (Figure 1). Irreversible $S_N2$-attack of the zirconocene-complexed alkoxide at C(6) provides an acyloxytetrahydrofuran **7**, but under kinetically controlled reaction conditions, addition at C(2) appears to be favored and leads to the 2,7,8-trioxabicyclo[3.2.1]octane skeleton **17**. Release of the cationic zirconocene complex closes the catalytic cycle.

**Scheme 3**

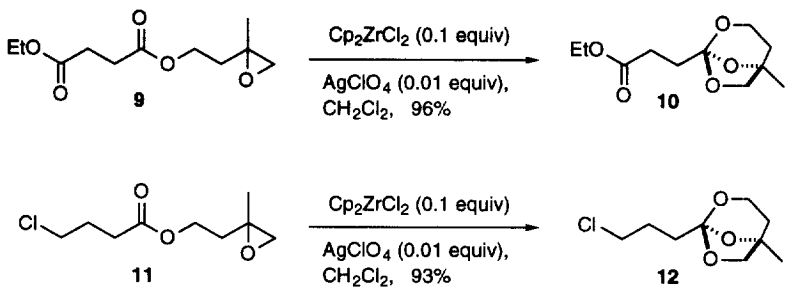
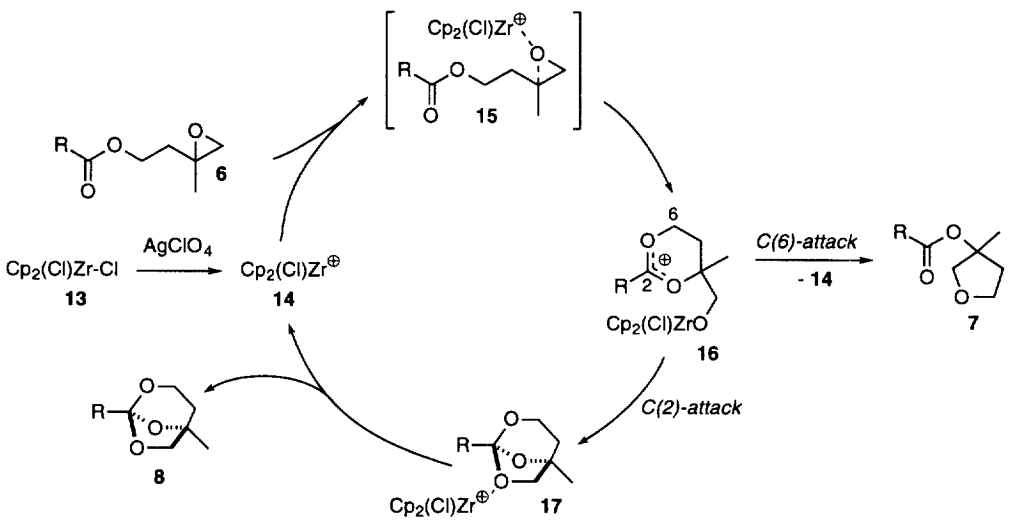
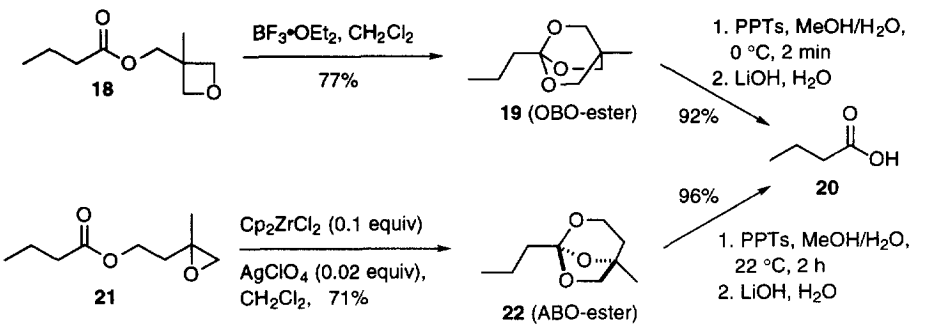



**Figure 1**



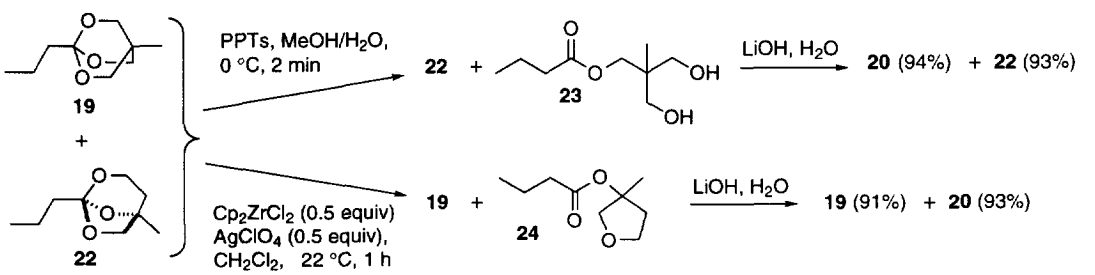

Mechanistically, this ortho ester formation is related to Corey's $BF_3$-catalyzed rearrangement of an acyloxetane to the 2,6,7-trioxabicyclo [2.2.2]octane (OBO-ester).[10] The OBO-ester **19** is derived from an oxetane **18**, and the epoxide-derived orthoester product **22** (ABO-ester) is an asymmetric isomer of this bicyclooctane motif. Both ortho esters are cleaved by exposure to mild acid followed by saponification (Scheme 4). Interestingly, there is a sufficiently high difference in the Brønsted- vs. Lewis-acid-lability of OBO-ester **19** and ABO-ester **22** to allow for an orthogonal protective group strategy. Exposure of a 1:1 mixture of **19** and **22** to 5 mol% PPTs in MeOH/$H_2O$ (40:1) at 0 °C for 2 min led to complete cleavage of the OBO-ester, and less than 5% cleavage of the ABO-ester was observed by $^1H$ NMR (Scheme 5). In contrast, exposure of the mixture of **19** and **22** to 0.5 equiv of *in situ* prepared $Cp_2(Cl)Zr^{\oplus}$ led to a selective rearrangement of the ABO-ester to the tetrahydrofuran **24**,[6] without affecting the OBO-ester **19**.

**Scheme 4**




Both esters **23** and **24** can be further treated with base to release the acid **20** in yields of 94% and 93%, respectively, a procedure which does not affect the remaining ortho ester derivatives **22** and **19**, which were recovered in 93% and 91% yield. Similarly, selective cleavage of a mixture of **19** and ABO-ester **25** was possible in high yield. Accordingly, our ABO-ester method establishes a novel orthogonal protective group strategy for carboxylic acids. Whereas cyclic ortho esters are generally more stable than their acyclic counterparts, an orthogonal protection has not yet been achieved with purely alcohol-derived ortho esters.[11-15] The ABO-ester fills this gap in the protection strategy for the carboxyl group (Figure 2).

**Scheme 5**



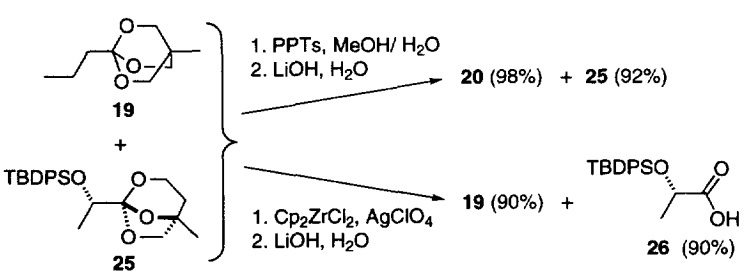
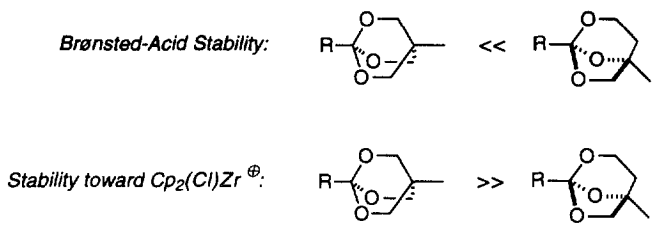



**Figure 2**




The mild conditions for the zirconocene-catalyzed ortho ester formation are especially useful for the formation of ortho esters of polyfunctionalized carboxylic acids. Condensation of *N*-protected glycine **27** with epoxy alcohol **28** in the presence of dicyclohexylcarbodiimide (DCC) and dimethylaminopyridine (DMAP) followed by treatment with 10 mol% of $Cp_2ZrCl_2$ and 2 mol% of $AgClO_4$ led to the amino acid ortho ester **30** (Scheme 6). More importantly, the L-serine derivative **31** did not require protection of the side-chain hydroxyl function and was converted to the analogous orthoester **32** with less than 1% overall racemization at the α-carbon as indicated by Mosher ester analysis (Scheme 6).[16] This reaction scheme was readily extended to the protection of other amino acid carboxylates. Acid-sensitive functions such as the Boc-carbamate as well as silyl ethers are fully compatible with the reaction conditions (Table 1). All ABO-derivatives shown are derived from racemic epoxy alcohol, and are, accordingly, 1:1 mixtures of diastereomers at ortho ester C(1) and C(5) positions.

**Scheme 6**

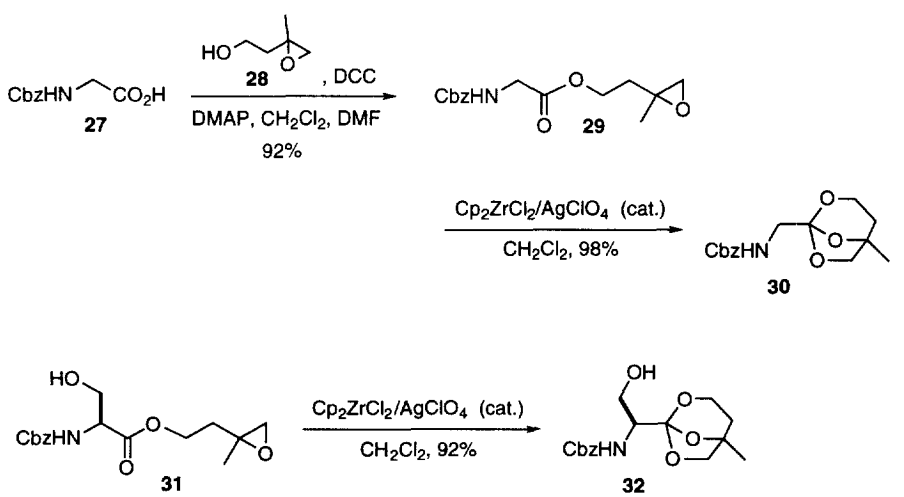
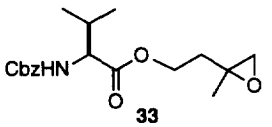
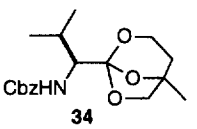
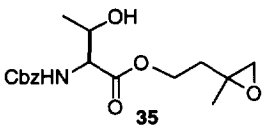
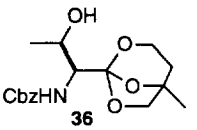
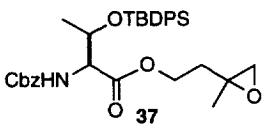
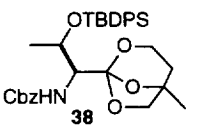
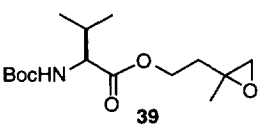
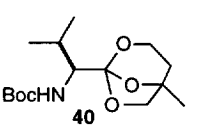
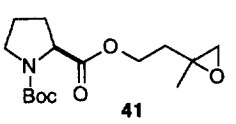
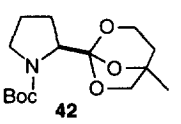
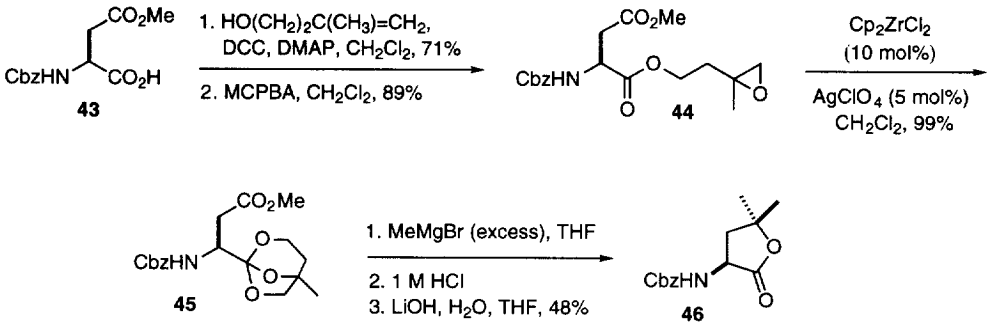


**Table 1.** Preparation of amino acid ABO-esters by cationic zirconocene-catalyzed rearrangement of epoxy esters.

| Epoxy Ester | Ortho Ester | Yield [%] |
|---|---|---|
|  **33** |  **34** | 91 |
|  **35** |  **36** | 100 |
|  **37** |  **38** | 96 |
|  **39** |  **40** | 96 |
|  **41** |  **42** | 90 |

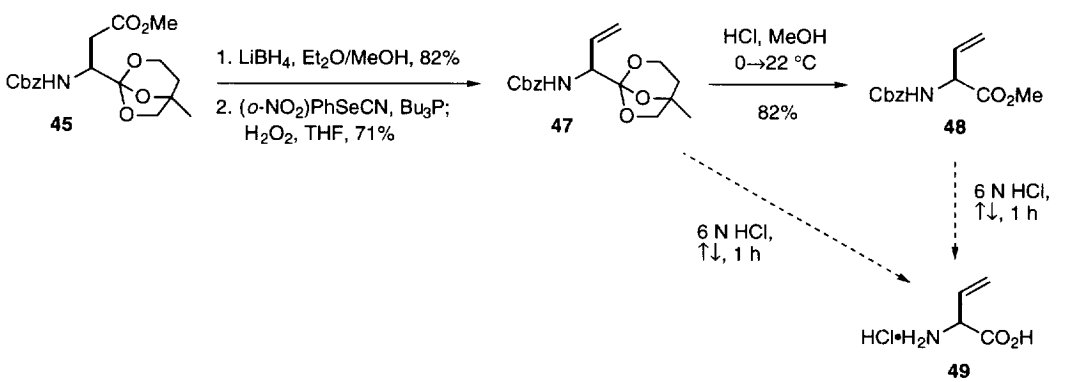
Ortho esters are ideal carboxyl protective groups against nucleophilic attack by hydroxide or organometallic reagents. Conversion of a carboxylate to an ortho ester is also an effective means to reduce the acidity of the α-hydrogen. These features are especially important for the manipulation of side-chain functionalized amino acid residues.[16] As an illustration for the use of ABO-esters in the stereoselective manipulation of amino acid building blocks, we have developed efficient protocols for the preparation of L-γ-hydroxyleucine lactone **46** and α-vinyl glycine **48** from L-aspartic acid. For both target molecules, ortho ester **45** served as an intermediate. This compound is readily available in 63% overall yield from *N*-Cbz-protected aspartyl ester **43** (Scheme 7). Exposure of **45** to an excess of methyl Grignard reagent, followed by acidic hydrolysis of the resulting tertiary alcohol in 1 M HCl and ester saponification provided the γ-lactone **46** in 48% yield. γ-Hydroxyleucine **46** is a component of toxins of the green death-cap mushroom *Amanito phalloides*. Previously this compound has been prepared by photochlorination of leucine,[17] and our route offers improved ease of access and flexibility for variation of γ-alkyl substituents.

**Scheme 7**




α-Vinylglycine is also a mushroom component and has been used as a mechanism-based enzyme inhibitor.[18] Previous asymmetric syntheses of this non-proteinogenic amino acid have started from methionine,[19] glutamic acid,[20,21] serine,[22] homoserine,[23,24] D-mannitol,[25] and cyclo(valylglycine)[26] or used enzymatic resolution.[18] Reduction of the aspartate derived ortho ester **45** with $LiBH_4$, followed by Grieco-elimination[27] provided the fully protected vinylglycine building block **47**. As expected, ortho ester **47** does not exhibit the well-known tendency of vinylglycine for migration of the double bond or racemization under basic conditions. Exposure to acidic methanol smoothly converted the ortho ester to vinylglycine methyl ester **48**. Ester **48** has been converted to vinylglycine hydrochloride (**49**) in quantitative yield in 6 N HCl,[19a,b,20,21] suggesting that ortho ester **47** could be directly converted to optically pure **49** under these conditions.[28]

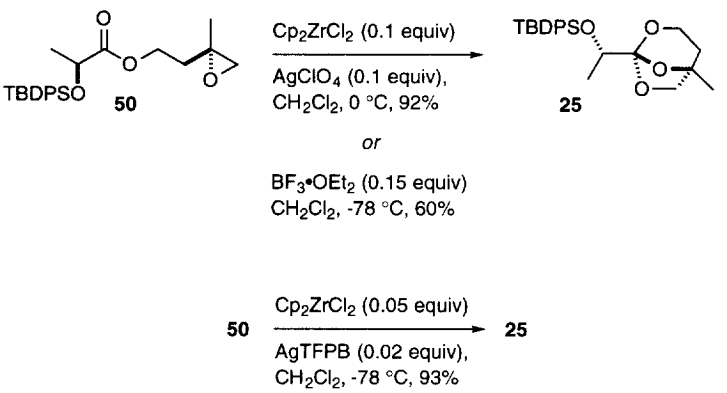
**Scheme 8**




The ease of cationic zirconocene-catalyzed formation of 2,7,8-trioxabicyclo[3.2.1]octane ortho esters from amino acids also extends to other α-functionalized carboxylates. Treatment of the (*S*)-lactate derivative **50** with catalytic $Cp_2ZrCl_2/AgClO_4$ at 0 °C provided ortho ester **25** as a single stereoisomer in 92% yield (Scheme 9). The use of $BF_3$-etherate for this process generally leads to considerably lower yields: 60% of **25** were obtained at -78 °C, and higher temperatures led to extensive decomposition of starting material and ortho ester product. If desired, an increase in the reactivity of the cationic zirconocene catalyst can be achieved by substitution of the weakly co-

ordinating anion $ClO_4^-$ with the "non-coordinating" tetraarylborate $B(3,5\text{-}C_6H_3(CF_3)_2)_4^-$ ($TFPB^-$).[29,30] In the presence of 5 mol% of zirconocene dichloride and 2 mol% of AgTFPB,[31] epoxy ester **50** was smoothly converted to ABO-ester **25** in 93% yield within 6 h at -78 °C. In toluene the reaction proceded somewhat more slowly, and 93% of **25** were isolated after 18 h at -78 °C. The conversions of **50** to **25** as a single isomer underline the high level of stereoselectivity in the neighbouring group assisted opening of epoxy ester shown in Figure 1 and represent the first convenient and general protocol for the asymmetric synthesis of ortho esters.[32,33]

**Scheme 9**




## Conclusions

Ortho esters are among the few carboxylic acid protective groups that demonstrate a high level of stabillity toward strong nucleophiles and bases. Compared to a carboxylic acid, the ortho ester removes the acidic hydroxyl group as well as the electrophilic carbonyl function and reduces the acidity of the α-hydrogens by many orders of magnitude. Historically, a broad use of ortho esters has been complicated by the difficulty and low yields in their preparation from acids or nitriles and alcohols.[14,15] Corey's OBO-ester protocol,[10] the $BF_3$-etherate mediated preparation of the 2,6,7-trioxabicyclo [2.2.2]octane ring system from oxetanyl esters, greatly facilitated the synthesis of ortho esters of functionalized carboxylates and stimulated their use as protective groups in organic synthesis.[11] The cationic zirconocene-catalyzed rearrangement of epoxy esters to give 2,7,8-trioxabicyclo[3.2.1]octanes (ABO-esters) adds a new variant to this protective group strategy. We have been able to demonstrate that ABO-esters are readily obtained in very high yields from functionalized and acid-sensitive substrates using *in situ* prepared cationic zirconocene. Mild acid hydrolysis followed by saponification regenerates the carboxylate without epimerization of α-stereocenters in amino and hydroxy acids. Alcoholysis of the ortho ester leads directly to the corresponding alkyl ester. The syntheses of the mushroom components (*S*)-γ-hydroxyleucine lactone and (*S*)-α-vinylglycine demonstrate the versatility of this protocol.

In combination with the OBO-ester, the ABO-ester establishes for the first time an orthogonal protective group strategy for ortho esters. Bicyclo[3.2.1] ABO-esters are considerably more Brønsted acid-stable than the bicyclo[2.2.2] OBO-ester derivatives. In contrast, prolonged exposure of ABO-

ester to cationic zirconocene leads to a secondary rearrangement to an acyloxytetrahydrofuran, which can be further cleaved in the presence of an OBO-ester moiety. We expect that these new methods in addition to the asymmetric synthesis of chiral ABO-esters using readily available chiral epoxy alcohol derivatives will greatly stimulate further applications of bicyclic ortho esters in organic chemistry.

## Experimental Section

**General.** Anhydrous solvents were freshly distilled from either sodium benzophenone ketyl, $P_2O_5$, or $CaH_2$. All reactions were performed in oven-dried glassware under an argon or nitrogen atmosphere. IR spectra were recorded on an IBM IR/32 spectrophotometer. NMR spectra were recorded in $CDCl_3$ unless stated otherwise on a Bruker AC-300 NMR spectrometer (300 MHz for $^1H$ NMR and 75 MHz for $^{13}C$ NMR) and are reported in ppm relative to tetramethylsilane (δ). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad), integration, and coupling constants. Mass spectra were obtained on a VG-70-70 HF. Analytical TLC used Merck silica gel 60 F-254 plates, and flash chromatography on $SiO_2$ or florisil was used to separate and purify the crude reaction mixtures. Commercially available anhydrous $AgClO_4$ was used without special precautions. **CAUTION**: Anhydrous $AgClO_4$, especially solvated crystals containing organic compounds, can explode when struck. $AgClO_4$ is also hygroscopic and light sensitive, decomposes at or above 450 °C, and explodes readily at 800 °C. Several companies, including Aldrich and Strem, offer anhydrous $AgClO_4$; most suppliers of fine chemicals offer silver perchlorate monohydrate which can be dried by azeotropic distillation. $AgAsF_6$ has been suggested as a safe, but ca. 10x more expensive alternative to $AgClO_4$,[34] and all reactions reported here in this paper work equally well for either of the two silver salts. Alternatively, $AgClO_4$ monohydrate can also be used but reactions proceed more slowly. For example, using catalytic $AgClO_4$ monohydrate in place of commercially available "anhydrous" $AgClO_4$ for the formation of **25** from **50** led to an increase in the reaction time from 10 min to 1 h, after which 90% of the desired ortho ester was isolated.

**General procedure for epoxy ester formation. Succinic acid ethyl ester 2-(2-methyloxiranyl)ethyl ester (9).** A solution of 150 mg (1.74 mmol) of 3-methyl-3-buten-1-ol in 3 mL of $CH_2Cl_2$ was cooled in an ice bath and treated with 290 mg (1.74 mmol) of ethyl succinyl chloride. A solution of 350 mg (3.48 mmol) of $Et_3N$ in 1 mL of $CH_2Cl_2$ was then added dropwise. The reaction mixture was stirred at 0 °C for 15 min. $Et_2O$ was added and the mixture was washed with 1 M aqueous HCl solution, 5% aqueous $NaHCO_3$ solution and $H_2O$. The organic layer was dried ($Na_2SO_4$) and concentrated *in vacuo*. The residue was chromatographed on $SiO_2$ (EtOAc/hexanes, 1:10) to give 340 mg (91%) of succinic acid ethyl ester 3-methylbut-3-enyl ester as a colorless oil: IR (neat) 2956, 1724, 1691, 1450, 1367, 1153, 1024, 887 $cm^{-1}$; $^1H$ NMR δ 4.75 (s, 1 H), 4.68 (s, 1 H), 4.16 (t, 2 H, $J$ = 6.8 Hz), 4.09 (q, 2 H, $J$ = 7.1 Hz), 2.57 (s, 4 H), 2.29 (t, 2 H, $J$ = 6.8 Hz), 1.70 (s, 3 H), 1.21 (t, 3 H, $J$ = 7.1 Hz); $^{13}C$ NMR δ 172.4, 141.7, 112.4, 62.9, 60.7, 36.7, 29.2, 22.6, 14.3; MS (EI) *m/z* (relative intensity) 169 ([M-$C_2H_5O$]$^+$, 2), 129 (25), 101 (65), 68 (100); HRMS (EI) *m/z* calcd. for $C_9H_{13}O_3$ (M-$C_2H_5O$): 169.0865, found: 169.0856.

A solution of 275 mg (1.14 mmol) of succinic acid ethyl ester 3-methylbut-3-enyl ester in 5 mL of $CH_2Cl_2$ was treated portionwise with 430 mg of mCPBA (1.37 mmol, 55%) at 0 °C. The mixture was stirred at 22 °C for 4 h and then cooled to 0 °C. The cold mixture was filtered, and the filtrate was

washed with 5% aqueous KOH solution and brine. The organic layer was dried ($Na_2SO_4$) and concentrated *in vacuo*. The residue was chromatographed on $SiO_2$ (EtOAc/hexanes, 1:5) to give 244 mg (93%) of **9** as a colorless oil: IR (neat) 2951, 1714, 1450, 1431, 1361, 1151, 1018 $cm^{-1}$; $^1H$ NMR δ 4.19-4.03 (m, 4 H), 2.55 (s, 4 H), 2.58-2.48 (m, 2 H), 1.91-1.76 (m, 2 H), 1.28 (s, 3 H), 1.18 (t, 3 H, $J$ = 7.1 Hz); $^{13}C$ NMR δ 172.3, 61.2, 60.7, 54.9, 53.6, 35.6, 29.1, 21.3, 14.2; MS (EI) *m/z* (relative intensity) 185 ([M- $C_2H_5O$]$^+$, 3), 129 (55), 101 (100), 85 (40); HRMS (EI) *m/z* calcd. for $C_9H_{13}O_4$ (M-$C_2H_5O$): 185.0814, found: 185.0805.

**1-[2-(Ethoxycarbonyl)ethyl]-5-methyl-2,7,8-trioxobicyclo[3.2.1]octane (10).** A solution of 230 mg (1.0 mmol) of succinate **9** in 8 mL of $CH_2Cl_2$ was treated at 20 °C with 29 mg (0.10 mmol, 0.10 equiv) of $Cp_2ZrCl_2$ and 2 mg (0.01 mmol, 0.01 equiv) of $AgClO_4$. The reaction mixture was stirred at 20 °C for 15 min, poured into saturated aqueous $NaHCO_3$ solution, and extracted with EtOAc (3x). The combined organic layers were dried ($Na_2SO_4$), filtered through $SiO_2$, and concentrated *in vacuo*. The oily residue was purified by chromatography on $SiO_2$ (EtOAc/hexanes, 1 : 4) to give 220 mg (96%) of **10** as a colorless oil: IR (neat) 2978, 2887, 1734, 1444, 1373, 1327, 1265, 1180, 1142, 1076, 1057, 1012, 908 $cm^{-1}$; $^1H$ NMR δ 4.11 (q, 2 H, $J$ = 7.1 Hz), 4.07 (dd, 1 H, $J$ = 11.3, 4.1 Hz), 4.01 (d, 1 H, $J$ = 7.1 Hz), 3.85 (dd, 1 H, $J$ = 11.3, 6.6 Hz), 3.48 (dd, 1 H, $J$ = 7.1, 2.2 Hz), 2.49-2.44 (m, 2 H), 2.20-2.15 (m, 2 H), 2.07-1.96 (m, 1 H), 1.43 (dd, 1 H, $J$ = 13.3, 4.3 Hz), 1.35 (s, 3 H), 1.23 (t, 3 H, $J$ = 7.1 Hz); $^{13}C$ NMR δ 173.2, 120.1, 78.8, 74.0, 60.4, 59.2, 33.8, 30.7, 28.9, 22.0, 14.3; MS (EI) *m/z* (relative intensity) 185 ([M-OEt]$^+$, 10), 147 (8), 129 (85), 101 (100), 85 (40), 55 (20), 43 (30); HRMS (EI) *m/z* calcd. for $C_9H_{13}O_4$ (M-OEt): 185.0814, found: 185.0814.

**1-(3-Chloropropyl)-5-methyl-2,7,8-trioxobicyclo[3.2.1]octane (12).** According to the procedure used for **10**, 200 mg (0.97 mmol) of chlorobutyrate **11**, 28 mg (0.097 mmol) of $Cp_2ZrCl_2$ and 2 mg (0.01 mmol) of $AgClO_4$ afforded 185 mg (93%) of **12** as a colorless oil: IR (neat) 2974, 2887, 1732, 1446, 1392, 1383, 1329, 1263, 1194, 1174, 1142, 1057, 1012, 974, 910, 889 $cm^{-1}$; $^1H$ NMR δ 4.00 (dd, 1 H, $J$ = 11.8, 4.3 Hz), 3.95 (d, 1 H, $J$ = 7.2 Hz), 3.77 (dd, 1 H, $J$ = 11.8, 6.7 Hz), 3.53-3.49 (m, 2 H), 3.43 (dd, 1 H, $J$ = 7.1, 2.0 Hz), 2.00-1.88 (m, 5 H), 1.39 (dd, 1 H, $J$ = 13.2, 4.3 Hz), 1.30 (s, 3 H); $^{13}C$ NMR δ 120.2, 78.6, 73.7, 59.0, 44.8, 33.7, 32.7, 26.8, 21.9; MS (EI) *m/z* (relative intensity) 176 ([M-$CH_2O$]$^+$, 15), 144 (6), 114 (6), 105 (100); HRMS (EI) *m/z* calcd. for $C_8H_{13}ClO_2$ (M-$CH_2O$) 176.0604, found 176.0620.

**4-Methyl-1-propyl-2,6,7-trioxabicyclo[2.2.2]octane (19).** To a solution of 100 mg (0.58 mmol) of butyric acid 3-methyloxetan-3-ylmethyl ester (**18**) in 0.6 mL of dry $CH_2Cl_2$ at -15 °C was added 18 μL (0.14 mmol) of boron trifluoride diethyl etherate. After stirring for 18 h at -15 °C, the mixture was quenched by addition of 80 μL (0.58 mmol) of triethylamine, diluted with $Et_2O$ and filtered to remove the amine-boron trifluoride complex. The filtrate was concentrated and chromatographed on florisil ($Et_2O$/pentane, 1 : 6) to give 77 mg (77%) of **19** as a white wax: Mp 38-39 °C; $^1H$ NMR δ 3.87 (s, 6 H), 1.65-1.59 (m, 2 H), 1.47-1.39 (m, 2 H), 0.87 (t, 3 H, $J$ = 7.5 Hz), 0.78 (s, 3 H); $^{13}C$ NMR δ 109.0, 72.6, 38.8, 30.3, 16.6, 14.6, 14.1.

**5-Methyl-1-propyl-2,7,8-trioxabicyclo[3.2.1]octane (22).** A solution of 100 mg (0.58 mmol) of epoxy ester **21** in 2.5 mL of dry $CH_2Cl_2$ was treated at 0 °C with 8 mg (0.03 mmol) of $Cp_2ZrCl_2$ and 2 mg (0.01 mmol) of anhydrous $AgClO_4$. The reaction mixture was stirred at 0 °C for 10 min. Saturated aqueous $NaHCO_3$ solution was added and the mixture was extracted with $Et_2O$ (3x). The combined ether layers were dried ($Na_2SO_4$) and concentrated *in vacuo*. The residue was chromatographed on florisil (EtOAc/hexanes, 1 : 10) to give 71 mg (71%) of **22** as a colorless oil: $^1H$ NMR δ 4.07 (dd, 1 H, $J$ = 12.3, 4.3 Hz), 4.00 (d, 1 H, $J$ = 7.0 Hz), 3.82 (dd, 1 H, $J$ = 11.4, 6.7 Hz), 3.48

(dd, 1 H, $J$ = 7.1, 2.1 Hz), 2.03-1.94 (m, 1 H), 1.80-1.72 (m, 2 H), 1.54-1.39 (m, 3 H), 1.35 (s, 3 H), 0.90 (t, 3 H, $J$ = 7.3 Hz); $^{13}C$ NMR δ 120.8, 78.6, 73.8, 59.1, 37.6, 33.9, 22.1, 16.8, 14.1.

**General Protocol for Ortho Ester Hydrolysis. Butyric acid (20).** A solution of 50 mg (0.29 mmol) of OBO-ester **19** in 3 mL of MeOH/$H_2O$ (40 : 1) was treated at 0 °C with 3 mg (0.015 mmol) of pyridinium p-toluenesulfonate. The mixture was stirred at 0 °C for 2 min, diluted with EtOAc and washed with saturated aqueous $NaHCO_3$ solution. The solvent was evaporated and the residue was dissolved in 3 mL of THF. After addition of 3 mL of 1 M aqueous LiOH solution the reaction mixture was stirred for 6 h at 22 °C. THF was evaporated and the aqueous layer was washed with EtOAc and acidified with 3 M aqueous HCl solution to pH 1. The acidic solution was extracted with $Et_2O$ (3x). The combined ether layers were dried ($Na_2SO_4$) and concentrated *in vacuo* to give 23 mg (92%) of **20**.

According to the same protocol, 50 mg (0.29 mmol) of ABO-ester **22** were treated with 3 mg of pyridinium p-toluenesulfonate for 1.5 h at 22 °C followed by LiOH hydrolysis to give 24 mg (96%) of butyric acid.

**Selective hydrolysis of OBO- and ABO-esters. Method A. Hydrolysis of OBO-ester 19 in the presence of ABO-ester 22.** A solution of 20 mg (0.116 mmol) of OBO-ester **19** and 20 mg (0.116 mmol) of ABO-ester **22** in 2 mL of MeOH/$H_2O$ (40:1) was treated at 0 °C with 1.5 mg (0.006 mmol) of pyridinium *p*-toluenesulfonate. The reaction mixture was stirred at 0 °C for 2 min, diluted with $Et_2O$ and washed with saturated aqueous $NaHCO_3$ solution. The solvent was evaporated and the residue was dissolved in 2 mL of THF. After the addition of 2 mL of 1 M aqueous LiOH solution, the mixture was stirred for 6 h at 22 °C. Solvent was evaporated and the aqueous layer was extracted with $Et_2O$ (3x). The combined ether layers were dried ($Na_2SO_4$) and concentrated *in vacuo* to give 18.7 mg (93%) of **22**. The aqueous layer was acidified to pH 1 by addition of 3 M aqueous HCl solution, and extracted with $Et_2O$ (3x). The combined ether layers were dried ($Na_2SO_4$) and concentrated *in vacuo* to give 9.6 mg (94%) of butyric acid **20**.

**Hydrolysis of OBO-ester 19 in the presence of ABO-ester 25.** A solution of 10 mg (0.058 mmol) of OBO-ester **19** and 24 mg (0.058 mmol) of ABO-ester **25** in 1 mL of MeOH/$H_2O$ (40:1) was treated at 0 °C with 0.7 mg (2.9 μmol) of pyridinium *p*-toluenesulfonate. The mixture was stirred at 0 °C for 2 min, diluted with $Et_2O$ and washed with saturated aqueous $NaHCO_3$ solution. The solvent was evaporated, the residue was dissolved in 1 mL of THF, and 1 mL of 1 M aqueous LiOH solution was added. The reaction mixture was stirred for 6 h at 22 °C, solvent was evaporated, and the aqueous layer was extracted with $Et_2O$ (3x). The combined ether layers were dried ($Na_2SO_4$) and concentrated *in vacuo* to give 22.1 mg (92%) of **25**. The aqueous layer was acidified to pH 1 by addition of 3 M aqueous HCl solution, and extracted with $Et_2O$ (3x). The combined ether layers were dried ($Na_2SO_4$) and concentrated *in vacuo* to give 5.0 mg (98%) of butyric acid **20**.

**Method B. Hydrolysis of ABO-ester 22 in the presence of OBO-ester 19.** A solution of 20 mg (0.116 mmol) of **19** and 20 mg (0.116 mmol) of **22** in 2 mL of dry $CH_2Cl_2$ was treated at 0 °C with 16 mg (0.058 mmol) of zirconocene dichloride followed by 12 mg (0.058 mmol) of anhydrous silver perchlorate. The mixture was stirred at 22 °C for 1 h, treated with aqueous $NaHCO_3$ solution and extracted with $Et_2O$ (3x). The combined organic layers were dried ($Na_2SO_4$) and concentrated *in vacuo*. The residue was dissolved in 2 mL of THF, treated with 2 mL of 1 M aqueous LiOH solution and stirred for 6 h at 22 °C. The organic solvent was evaporated and the aqueous layer was extracted with $Et_2O$ (3x). The combined ether layers were dried ($Na_2SO_4$) and concentrated *in vacuo* to give 18.2 mg (91%) of **19**. The aqueous layer was acidified to pH 1 by addition of 3 M aqueous HCl

solution, and extracted with $Et_2O$ (3x). The combined ether layers were dried ($Na_2SO_4$) and concentrated *in vacuo* to give 9.5 mg (93%) of butyric acid **20**.

**Hydrolysis of ABO-ester 25 in the presence of OBO-ester 19.** A solution of 10 mg (0.058 mmol) of **19** and 24 mg (0.058 mmol) of **25** in 1 mL of dry $CH_2Cl_2$ was treated at 0 °C with 8.5 mg (0.029 mmol) of zirconocene dichloride followed by 6 mg (0.029 mmol) of anhydrous silver perchlorate. The mixture was stirred at 22 °C for 1 h. Saturated aqueous $NaHCO_3$ solution was added and the mixture was extracted with $Et_2O$ (3x). The combined ether layers were concentrated, the residue was dissolved in 1 mL of THF and 1 mL of 1 M aqueous LiOH solution, and the reaction mixture was stirred for 4 h at 22 °C. Solvent was evaporated and the aqueous layer was extracted with $Et_2O$ (3x). The combined ether layers were dried ($Na_2SO_4$) and concentrated *in vacuo* to give 9.0 mg (90%) of **19**. The aqueous layer was acidified to pH 4 by addition of 3 M aqueous HCl solution, and extracted with $Et_2O$ (3x). The combined ether layers were dried ($Na_2SO_4$) and concentrated *in vacuo* to give 17 mg (90%) of (2*S*)-2-(tert-butyldiphenylsilanyloxy)propionic acid **26**.

***tert*-Butyl-{(1*S*)-1-[(1*S*,5*R*)-5-methyl-2,7,8-trioxabicyclo[3.2.1]oct-1-yl}diphenylsilane (25). Method A.** A solution of 12 mg (0.029 mmol) of (2*S*)-2-(*tert*-butyldiphenylsilanyloxy)propionic acid 2-[(2*S*)-2-methyloxiranyl]ethyl ester (**50**) in 0.5 mL of dry $CH_2Cl_2$ was treated at 0 °C with 1 mg (0.003 mmol) of $Cp_2ZrCl_2$ and 0.6 mg (0.002 mmol) of anhydrous $AgClO_4$. The reaction mixture was stirred at 0 °C for 15 min. Saturated aqueous $NaHCO_3$ solution was added and the mixture was extracted with $Et_2O$ (3x). The combined ether layers were dried ($Na_2SO_4$) and concentrated *in vacuo*. The residue was chromatographed on florisil (EtOAc/hexanes, 1 : 10) to give 11 mg (92%) of **25** as a colorless oil: $[\alpha]_D$ +14.2 (*c* 0.6, $CHCl_3$); IR (neat) 2920, 1130, 1020, 933, 700 $cm^{-1}$; $^1H$ NMR δ 7.75-7.70 (m, 4 H), 7.40-7.33 (m, 6 H), 4.05 (dd, 1 H, *J* = 11.4, 3.8 Hz), 4.00-3.90 (m, 2 H), 3.81 (dd, 1 H, *J* = 11.3, 6.6 Hz), 3.41 (dd, 1 H, *J* = 7.0, 2.1 Hz), 2.03-1.97 (m, 1 H), 1.42 (dd, 1 H, *J* = 13.2, 4.0 Hz), 1.36 (s, 3 H), 1.17 (d, 3 H, *J* = 6.5 Hz), 1.06 (s, 9 H); $^{13}C$ NMR δ 136.3, 134.4, 129.4, 127.4, 127.2, 120.5, 78.7, 73.8, 69.8, 59.0, 34.1, 27.1, 22.0, 19.5, 18.3; MS (EI) *m/z* (relative intensity) 412 ($M^+$, 2), 355 (50), 283 (75), 199 (85), 175 (25), 85 (100); HRMS (EI) *m/z* calcd. for $C_{24}H_{32}O_4Si$ 412.2070, found 412.2076.

**Method B.** A solution of 20 mg (0.049 mmol) of **50** in 0.5 mL of dry $CH_2Cl_2$ was treated at -78 °C with 1 μL (0.007 mmol) of boron trifluoride diethyl etherate. The reaction mixture was stirred at -78 °C for 2 min. Saturated aqueous $NaHCO_3$ solution was added and the mixture was stirred at 22 °C for 5 min, and extracted with $Et_2O$ (3x). The combined organic layers were dried ($Na_2SO_4$) and concentrated *in vacuo*. The residue was chromatographed on florisil (EtOAc/hexanes, 1:10) to give 12 mg (60%) of **25**.

**Method C.** A solution of 30 mg (0.073 mmol) of **50** in 0.7 mL of dry $CH_2Cl_2$ was cooled to -78 °C and treated with 1 mg (0.0036 mmol) of zirconocene dichloride and 14 μL (0.0014 mmol) of silver tetrakis[3,5-bis(trifluoromethyl)phenyl]borate (0.1 M solution in $Et_2O$). The reaction mixture was stirred at -78 °C for 6 h, quenched with saturated aqueous $NaHCO_3$ solution, and extracted with $Et_2O$ (3x). The combined organic layers were dried ($Na_2SO_4$) and concentrated *in vacuo*. The residue was chromatographed on florisil (EtOAc/hexanes, 1:10) to give 28 mg (93%) of **25**.

**(2*S*)-2-(tert-Butyldiphenylsilanyloxy)propionic acid (26).** Commercial (*S*)-(+)-lactic acid (10 mmol) in 10 mL of DMF was treated at 0 °C with 5.7 g (21 mmol) of tert-butyldiphenylchlorosilane and 1.7 g (25 mmol) of imidazole. The reaction mixture was stirred at 22 °C for 4 h, diluted with $H_2O$ (100 mL), and extracted with $Et_2O$ (3x). The combined ether layers were washed with 1 M aqueous HCl solution, saturated aqueous $NaHCO_3$ solution, brine, and dried ($Na_2SO_4$). Evaporation of the solvent

gave 4.3 g of (2*S*)-2-(tert-butyldiphenylsilanyloxy)propionic acid tert-butyldiphenylsilanyl ester which was used without further purification.

A solution of 4.3 g of crude (2*S*)-2-(tert-butyldiphenylsilanyloxy)propionic acid tert-butyldiphenylsilanyl ester in 20 mL of MeOH and 6 mL of THF was treated with a solution of 2 g of $K_2CO_3$ in 6 mL of $H_2O$ and the mixture was stirred vigorously at 22 °C for 9 h. The reaction mixture was concentrated *in vacuo* to 1/4 of the volume and diluted with $H_2O$. The solution was acidified at 0 °C with 1 M aqueous $KHSO_4$ solution to pH 4-5 and extracted with EtOAc (3x). The combined organic layers were dried ($Na_2SO_4$) and concentrated *in vacuo*. The residue was purified by chromatography on $SiO_2$ (EtOAc/hexanes, 1:2) to give 2.1 g (64%) of **26** as a colorless oil: $[\alpha]_D$ -25.4° (*c* 1.4, $CHCl_3$); IR (neat) 3100, 2926, 1720, 1421, 1138, 1107, 1057, 736, 698 $cm^{-1}$; $^1H$ NMR δ 7.70-7.66 (m, 4 H), 7.49-7.31 (m, 6 H), 4.33 (q, 1 H, *J* = 6.8 Hz), 1.36 (d, 3 H, *J* = 6.8 Hz), 1.14 (s, 9 H); $^{13}C$ NMR δ 177.5, 135.8, 132.9, 132.2, 130.2, 127.9, 69.1, 26.9, 21.1, 19.3; MS (EI) *m/z* (relative intensity) 271 ([M-$C_4H_9$]$^+$, 40), 199 (100), 139 (45), 77 (10); HRMS (EI) *m/z* calcd. for $C_{15}H_{15}O_3Si$ (M- $C_4H_9$): 271.0790, found: 271.0787.

**Benzyloxycarbonylamino-acetic acid 2-(2-methyl-oxiranyl)-ethyl ester (29).** A solution of Cbz-Gly-OH (**27**, 200 mg, 0.96 mmol) in $CH_2Cl_2$/DMF (10 mL; 9 : 1) was added dropwise over 10 min to a cold (0 °C) solution of DCC (226 mg, 1.1 mmol), DMAP (5.8 mg, 0.048 mmol) and 3,4-epoxy-3-methylbutanol (112 mg, 1.1 mmol). After 1 h, the reaction mixture was warmed to room temperature and stirred for an additional 2 h. The solution was filtered to remove dicyclohexylurea, washed with 1% $NH_4Cl$ (2 x 50 mL), 5% $NaHCO_3$ (1 x 50 mL), $H_2O$ (2 x 50 mL), and saturated NaCl solution (1 x 50 mL), and dried ($Na_2SO_4$). The solution was concentrated *in vacuo* and purified by column chromatography on $SiO_2$ (EtOAc/hexanes, 1 : 2) to give **29** (257 mg, 92%) as an oily mixture of diastereomers: IR (neat) 3351, 3036, 2965, 1723, 1663, 1653, 1576, 1559, 1528, 1499, 1458, 1391, 1273, 1196, 1055, 1001, 907, 779, 741, 698 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 7.37-7.32 (m, 5 H), 5.24 (bs, 1 H), 5.13 (s, 2 H), 4.33-4.22 (m, 2 H), 3.99 (d, 2 H, *J* = 5.7 Hz), 2.64, 2.60 (AB, 2 H, *J* = 4.6 Hz), 1.99-1.86 (m, 2 H), 1.35 (s, 3 H); $^{13}C$ NMR ($CD_3OD$) δ 171.8, 159.1, 138.1, 129.5, 129.0, 128.9, 67.7, 62.7, 56.2, 54.5, 43.5, 36.5, 21.3; MS (EI) *m/z* (relative intensity) 293 ($M^+$, 1), 209 (2), 191 (1), 169 (2), 159 (1), 144 (1), 131 (1), 107 (50), 91 (100), 85 (50), 79 (20), 68 (20), 65(20), 55 (20), 51 (10), 43 (50); MS (CI) *m/z* 294 ([M+H]$^+$).

**General procedure for the synthesis of amino acid ortho esters from epoxy esters. (5-Methyl-2,7,8-trioxabicyclo[3.2.1]oct-1-yl methyl)-carbamic acid benzyl ester (30).** A solution of ester **29** (293 mg, 1.0 mmol) in $CH_2Cl_2$ (4 mL) was treated with $Cp_2ZrCl_2$ (28.8 mg, 0.1 mmol), and $AgClO_4$ (4 mg, 0.02 mmol). The reaction mixture was stirred for 4 h at room temperature, poured into saturated aqueous $NaHCO_3$ solution, and extracted with EtOAc (3 x 10 mL). The combined organic layers were dried ($Na_2SO_4$), filtered ($SiO_2$), and concentrated in *vacuo*. The residue was purified by column chromatography on $SiO_2$ (EtOAc/hexanes, 1 : 1) to give **30** (287 mg, 98%) as an oil: IR (neat) 3359, 2953, 2890, 1723, 1528, 1455, 1401, 1383, 1331, 1239, 1194, 1146, 1102, 1055, 1007, 938, 887, 776, 741, 698 $cm^{-1}$; $^1H$ NMR ($CDCl_3$ ) δ 7.36-7.30 (m, 5 H), 5.12 (s, 2 H), 5.02 (bs, 1 H) 4.10 (dd, 1 H, *J* = 11.5, 4.2 Hz), 4.03 (d, 1 H, *J* = 7.0 Hz), 3.88 (dd, 1 H, *J* = 11.5, 6.7 Hz), 3.58-3.50 (m, 3 H), 2.07- 2.01 (m, 1 H), 1.46 (dd, 1 H, *J* = 13.3, 4.2 Hz), 1.37 (s, 3 H); $^{13}C$ NMR ($CD_3OD$) δ 156.5, 136.6, 128.6, 128.2, 118.4, 79.2, 74.1, 66.9, 59.4, 44.3, 33.9, 21.9; MS (EI) *m/z* (relative intensity) 293 ($M^+$, 5), 265 (2), 209 (12), 191(2), 169 (2), 108 (100), 102 (15), 91 (100), 85 (100), 79 (20), 71 (35), 65 (25), 55 (20); HRMS (EI) calc. for $C_{15}H_{19}NO_5$ 293.1263, found 293.1261.

**(2*S*)-2-Benzyloxycarbonylamino-3-hydroxy-propionic acid 2-(2-methyl-oxiranyl)-ethyl ester (31).** A solution of Cbz-L-Ser-OH (47 mg, 0.20 mmol) in EtOAc (5 mL) was added dropwise

over 30 min to a cold (-40 °C) solution of DCC (49 mg, 0.24 mmol), DMAP (1.2 mg, 0.01 mmol) and 3,4-epoxy-3-methylbutanol (195 mg, 1.9 mmol). After 2 h, the reaction mixture was warmed to -20 °C and stirred for an additional 10 h. The solution was filtered, washed with 1% $NH_4Cl$ (2 x 30 mL), 5% $NaHCO_3$ (1 x 30 mL), $H_2O$ (3 x 30 mL), and saturated NaCl solution (1 x 50 mL), and dried ($Na_2SO_4$). The solution was concentrated *in vacuo* and purified by column chromatography on $SiO_2$ (EtOAc/hexanes, 1 : 1) to give **31** (52 mg, 82%) as an oily mixture of diastereomers: IR (neat) 3370, 3034, 2961, 1721, 1653, 1522, 1455, 1393, 1339, 1208, 1063, 907, 776, 741, 698 $cm^{-1}$; $^1H$ NMR ($CD_3OD$ ) δ 7.35-7.28 (m, 5 H), 5.10 (s, 2 H) 4.31-4.18 (m, 3 H), 3.91-3.78 (m, 2 H), 2.64-2.54 (m, 2 H), 1.96-1.79 (m, 2 H), 1.31 (s, 3 H); $^{13}C$ NMR ($CD_3OD$ ) δ 172.1, 158.4, 138.1, 129.4, 128.9, 67.7, 62.9, 57.9, 56.3, 54.5, 36.4, 21.3; MS (EI) *m/z* (relative intensity) 323 ($M^+$, 2), 293 (5), 248 (1), 239 (1), 150 (10), 108 (30), 91 (100), 79 (20), 68 (15), 55 (10); HRMS (EI) calcd. for $C_{15}H_{19}NO_5$ (M-$CH_2O$) 293.1263, found 293.1277.

**(1*S*)-[2-Hydroxy-1-(5-methyl-2,7,8-trioxabicyclo[3.2.1]oct-1-yl)-ethyl]-carbamic acid benzyl ester (32).** According to the general procedure, epoxyester **31** (320 mg, 1.0 mmol), $Cp_2ZrCl_2$ (28.8 mg, 0.1 mmol) and $AgClO_4$ (4 mg, 0.02 mmol) afforded **32** (294 mg, 92%) as an inseparable oily mixture of diastereomers: IR (neat) 3434, 2971, 2890, 1717, 1653, 1559, 1541, 1524, 1497, 1456, 1387, 1343, 1244, 1194, 1144, 1053, 1015, 885, 774, 741 $cm^{-1}$; $^1H$ NMR ($CD_3OD$) δ 7.35-7.27 (m, 5 H), 5.09, 5.08 (AB, 2 H, *J* = 15.0 Hz), 4.08-3.99 (m, 3 H), 3.86-3.78 (m, 2 H), 3.57-3.30 (m, 2 H), 2.01-1.91 (m, 1 H), 1.51 (dd, 1 H, *J* = 13.3, 4.1 Hz), 1.34, 1.32 (2s, 3 H ); $^{13}C$ NMR ($CD_3OD$ ) δ 159.1, 138.3, 129.4, 128.8, 120.3, 120.2, 80.4, 74.7, 67.5, 61.9, 60.4, 57.6, 34.7, 21.9; MS (EI) *m/z* (relative intensity) 323 ($M^+$, 3), 306 (1), 293 (3) 248 (3), 209 (3), 185 (6), 164 (5), 150 (7), 108 (30), 91 (100), 85 (50), 79 (20), 65 (10), 55 (10); HRMS (EI) calc. for $C_{16}H_{21}NO_6$ 323.1369, found 323.1383.

**(2*S*)-2-Benzyloxycarbonylamino-3-methyl-butyric acid 2-(2-methyl-oxiranyl)-ethyl ester (33).** A solution of Cbz-L-Val-OH (200 mg, 0.80 mmol) in $CH_2Cl_2$ (20 mL) was added dropwise over 1 h to a cold (-20 °C) solution of DCC (196 mg, 0.95 mmol), DMAP (4.9 mg, 0.04 mmol) and 3,4-epoxy-3-methylbutanol (97.5 mg, 0.95 mmol). The reaction mixture was stirred for 8 h at -20 °C, filtered, washed with 1% $NH_4Cl$ (2 x 30 mL), 5% $NaHCO_3$ (1 x 30 mL), $H_2O$ (2 x 30 mL), and saturated NaCl solution (1 x 50 mL), and dried ($Na_2SO_4$). The solution was concentrated *in vacuo* and purified by column chromatography on $SiO_2$ (EtOAc/hexanes, 1 : 3) to give **33** (243 mg, 91%) as an inseparable oily mixture of diastereomers: IR (neat) 3036, 2965, 2489, 1719, 1653, 1539, 1522, 1507, 1499, 1426, 1345, 1310, 1269, 1206, 1107, 1024, 905, 777, 741, 698 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 7.36-7.30 (m, 5 H), 5.26 (d, 1 H, *J* = 8.6 Hz), 5.11 (s, 2 H), 4.29-4.19 (m, 3 H), 2.64, 2.59 (AB, 2 H, *J* = 4.4 Hz), 2.21-2.11 (m, 1 H), 1.99-1.85 (m, 2 H), 1.34 (s, 3 H), 0.97 (d, 3 H, *J* = 6.8 Hz), 0.89 (d, 3 H, *J* = 6.9 Hz); $^{13}C$ NMR ($CD_3OD$) δ 173.4, 158.7, 138.2, 129.4, 129.0, 128.9, 67.6, 62.6, 61.2, 56.2, 54.5, 36.5, 31.6, 21.3, 19.6, 18.4; MS (EI) *m/z* (relative intensity) 335 ($M^+$, 4), 307 (2), 292 (2), 251 (4), 233 (3), 206 (50), 162 (100), 91 (10); HRMS (EI) calcd. for $C_{18}H_{25}NO_5$ 335.1733, found 335.1713.

**(1*S*)-[2-Methyl-1-(5-methyl-2,7,8-trioxabicyclo[3.2.1]oct-1-yl)-propyl]-carbamic acid benzyl ester (34).** According to the general procedure, epoxyester **33** (335 mg, 1.0 mmol), $Cp_2ZrCl_2$ (28.8 mg, 0.1 mmol), and $AgClO_4$ (4 mg, 0.02 mmol) afforded **34** (305 mg, 91%) as an inseparable oily mixture of diastereomers: IR (neat) 2963, 2888, 1725, 1509, 1466, 1458, 1387, 1350, 1306, 1264, 1219, 1194, 1148, 1127, 1096, 1053, 1021, 885, 739, 698 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 7.37-7.30 (m, 5 H), 5.13 (s, 2 H), 5.00, 4,95 (2d, 1 H, *J* = 10.6, 10.8 Hz), 4.06-3.84 (m, 4 H), 3.48, 3.41 (2dd, 1 H, *J* = 7.1, 2.2, 7.2, 2.2 Hz), 2.20-2.17 (m, 1 H), 2.04-2.00 (m, 1 H), 1.43 (dd, 1 H, *J* = 13.3, 4.1 Hz), 1.36, 1.34 (2s, 3 H), 0.96 (2d, 3 H, *J* = 7.0, 6.9 Hz), 0.88 (d, 3 H, *J* = 6.9 Hz); $^{13}C$ NMR ($CDCl_3$) δ

157.0, 136.8, 128.5, 128.3, 128.0, 127.6, 120.0, 79.2, 78.5, 74.0, 73.4, 66.7, 59.3, 59.2, 58.3, 58.1, 33.9, 28.1, 28.0, 22.0, 20.9, 16.9, 16.6; MS (EI) *m/z* (relative intensity) 335 ($M^+$, 5), 305 (2), 292 (3), 248 (7), 233 (3), 206 (20), 162 (30), 108 (25), 91 (100), 84 (60), 65 (10), 55 (15); HRMS (EI) calc. for $C_{18}H_{25}NO_3$ 335.1732, found 335.1748.

**(2*S*,3*R*)-2-Benzyloxycarbonylamino-3-hydroxy-butyric acid 2-(2-methyl-oxiranyl)-ethyl ester (35).** A solution of Cbz-L-Thr-OH (48 mg, 0.20 mmol) in $CH_2Cl_2$ (10 mL) was added dropwise over 30 min to a cold (-30 °C) solution of DCC (49 mg, 0.24 mmol), DMAP (1.2 mg, 0.01 mmol) and 3,4-epoxy-3-methylbutanol (195 mg, 1.9 mmol). After 1 h, the reaction mixture was warmed to -20 °C and stirred for an additional 8 h. The solution was filtered, washed with 1% $NH_4Cl$ (2 x 30 mL), 5% $NaHCO_3$ (1 x 30 mL), $H_2O$ (2 x 30 mL), and saturated NaCl solution (1 x 50 mL), and dried ($Na_2SO_4$). The solution was concentrated *in vacuo* and purified by column chromatography on $SiO_2$ (EtOAc/hexanes, 1 : 1) to give **35** (54 mg, 84%) as an inseparable oily mixture of diastereomers: IR (neat) 3650, 3629, 3436, 3036, 2975, 1723, 1653, 1522, 1456, 1393, 1267, 1210, 1067, 1028, 1005, 907, 880, 776, 741, 698 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 7.34-7.30 (m, 5 H), 5.69, 5.65 (2d, 1 H, *J* = 10.2, 10.7 Hz), 5.12 (s, 2 H) 4.50-4.36 (m, 2 H), 4.33-4.16 (m, 2 H), 3.30, 3.10 (2bs, 1 H), 2.62-2.58 (m, 2 H), 2.00-1.80 (m, 2 H), 1.37, 1.35 (2s, 3 H), 1.23 (d, 3 H, *J* = 6.4 Hz); $^{13}C$ NMR ($CDCl_3$ ) δ 171.1, 156.9, 136.3, 128.5, 128.2, 128.0, 67.6, 67.5, 67.1, 61.6, 61.5, 59.6, 55.6, 55.5, 53.5, 53.3, 35.5, 35.1, 20.5, 19.7, 19.6; MS (EI) *m/z* (relative intensity) 293 ([M-$C_2H_4O$]$^+$, 5), 224 (1), 204 (4), 164 (2), 107 (10), 100 (10), 91 (100), 85 (50), 79 (10), 65 (10), 56 (20); HRMS (EI) calcd. for $C_{15}H_{19}NO_5$ (M-$C_2H_4O$) 293.1263, found 293.1260.

**(1*S*,2*R*)-[2-Hydroxy-1-(5-methyl-2,7,8-trioxabicyclo[3.2.1]oct-1-yl)- propyl]-carbamic acid benzyl ester (36).** According to the general procedure except that the reaction mixture was stirred for 6 h, epoxyester **35** (325 mg, 1.0 mmol), $Cp_2ZrCl_2$ (28.8 mg, 0.1 mmol) and $AgClO_4$ (4 mg, 0.02 mmol) afforded **36** (325 mg, 100%) as an inseparable oily mixture of diastereomers: IR (neat) 3530, 3449, 2928, 2855, 1719, 1653, 1559, 1541, 1509, 1458, 1381, 1239, 1196, 1144, 1125, 1055, 1007, 887, 739, 698 $cm^{-1}$; $^1H$ NMR ($CDCl_3$ ) δ 7.35-7.26 (m, 5 H), 5.42, 5.39 (2d, 1 H, *J* = 8.9, 9.4 Hz), 5.13 (s, 2 H), 4.37-4.33 (m, 1 H), 4.10-4.03 (m, 2 H), 3.93-3.87 (m, 2 H), 3.54, 3.47 (2dd, 1 H, *J* =7.3, 2.0, 7.2, 2.1 Hz), 2.85, 2.75 (2s, 1 H), 2.10-2.00 (m, 1 H), 1.47 (dd, 1 H, *J* = 15.3, 2.0 Hz), 1.37, 1.36 (2s, 3 H ), 1.15 (d, 3 H, *J* = 6.4 Hz); $^{13}C$ NMR ($CDCl_3$ ) δ 156.9, 136.6, 128.4, 127.9, 127.5, 119.8, 79.4, 79.2, 73.9, 73.7, 66.8, 65.6, 59.4, 57.3, 57.1, 33.7, 21.8, 19.0; MS (EI) *m/z* (relative intensity) 293 ([M-$C_2H_4O$]$^+$, 20), 107 (10), 91 (100, 85 (50), 79 (10), 65 (10), 55 (10); HRMS (EI) calc. for $C_{15}H_{19}NO_5$ (M-$C_2H_4O$) 293.1263, found 293.1285.

**(2*S*,3*R*)-2-Benzyloxycarbonylamino-3-(*tert*-butyl-diphenylsilanyloxy)-butyric acid 2-(2-methyl-oxiranyl)-ethyl ester (37).** A solution of epoxyester **35** (50 mg, 0.15 mmol) in 3 mL of $CH_2Cl_2$ was treated at 0 °C with TBDPSCl (125 mg, 0.46 mmol), imidazole (51.7 mg, 0.46mmol) and DMAP (1.7 mg, 0.015 mmol). The reaction mixture was stirred for 12 h at 25 °C, and diluted with EtOAc (30 mL) and $H_2O$ (10 mL). The organic layer was washed with 0.5 N HCl solution (10 mL), $H_2O$ (2 x 20 mL) and saturated NaCl solution (1 x 20 mL), dried ($Na_2SO_4$), and concentrated *in vacuo*. Column chromatography on $SiO_2$ (EtOAc/hexanes, 1 : 6) gave **37** (81 mg, 93%) as an oily mixture of diastereomers: IR (neat) 2932, 2859, 1734, 1653, 1559, 1541, 1534, 1507, 1474, 1458, 1428, 1379, 1316, 1208, 1105, 1071, 961, 822, 741, 702 $cm^{-1}$; $^1H$ NMR ($CD_3OD$) δ 7.56-7.50 (m, 4 H), 7.35-7.18 (m, 11 H), 5.01 (s, 2 H), 4.29-4.25 (m, 1 H), 4.19-4.09 (m, 2 H), 4.02-3.93 (m, 1 H), 3.30 (s, 2 H), 1.75-1.62 (m, 2 H), 1.12 (d, 3 H, *J* = 5.3 Hz), 0.88 (s, 12 H); $^{13}C$ NMR ($CD_3OD$) δ 172.1, 158.9, 138.1, 137.1, 134.9, 134.1, 131.1, 131.0, 129.5, 129.1, 128.9, 128.7, 71.9, 71.4, 68.0, 62.8, 61.5, 54.0, 53.9, 38.2, 27.4, 25.3, 25.1, 21.0, 20.0; MS (CI) *m/z* 518 ([M-$C_3H_5O$]$^+$).

**(1*S*,2*R*)-[2-(*tert*-Butyl-diphenyl-silanyloxy)-1-(5-methyl-2,7,8-trioxa-bicyclo[3.2.1]oct-1-yl)-propyl]-carbamic acid benzyl ester Cbz-Thr(OTBDPS)-ortho ester (38).** According to the general procedure except that reaction mixture was stirred for 3 h, epoxyester **37** (283 mg, 0.5 mmol), $Cp_2ZrCl_2$ (14.4 mg, 0.05 mmol) and $AgClO_4$ (2 mg, 0.01 mmol) afforded **38** (271 mg, 96%) as an inseparable oily mixture of diastereomers: IR (neat) 2932, 2888, 2857, 1734, 1701, 1653, 1507, 1474, 1458, 1426, 1375, 1306, 1217, 1144, 1109, 1057, 1021, 953, 741, 702 $cm^{-1}$; $^1H$ NMR δ 7.82-7.71 (m, 4 H), 7.45-7.33 (m, 11 H), 5.53, 5.48 (2d, 1 H, $J$ = 10.5, 10.4 Hz), 5.21 (s, 2 H), 4.59, 4.58 (2dq, 1 H, $J$ = 2.0, 7.7 Hz), 4.01-3.89 (m, 2 H), 3.86-3.81 (m, 2 H), 3.47, 3.40 (2dd, 1 H, $J$ = 7.1, 2.0, 7.1, 1.9 Hz), 2.10-2.00 (m, 1 H), 1.47-1.36 (m, 1 H), 1.35, 1.33 (2s, 3 H), 1.09, 1.08 (2s, 9 H ), 1.02, 1.00 (2d, 3 H, $J$ = 6.4, 6.5 Hz); $^{13}C$ NMR δ 157.0, 136.9, 136.1, 136.0, 135.1, 135.0, 133.7, 129.5, 129.4, 128.5, 128.3, 128.0, 127.3, 119.3, 79.2, 78.4, 73.8, 73.3, 67.3, 66.7, 59.2, 59.1, 58.9, 58.7, 58.4, 33.8, 27.0, 21.9, 19.4; MS (EI) *m/z* (relative intensity) 575 ($M^+$, 1), 559 (1), 518 (7), 214 (2), 390 (1), 344 (2), 313 (1), 283 (3), 254 (7), 239 (3), 199 (13), 181 (5), 135 (12), 91 (100), 57 (15); HRMS (EI) calc. for $C_{29}H_{32}NO_6Si$ ($M-C_4H_9$) 518.1999, found 518.1915.

**(2*S*)-2-*tert*-Butoxycarbonylamino-3-methyl-butyric acid 2-(2-methyl-oxiranyl)-ethyl ester (39).** According to the procedure used for **33**, Boc-L-Val-OH (174 mg, 0.80 mmol), DCC (196 mg, 0.95 mmol), DMAP (4.9 mg, 0.04 mmol) and 3,4-epoxy-3-methylbutanol (97.5 mg, 0.95 mmol) afforded **39** (224 mg, 93%) as an inseparable oily mixture of diastereomers: IR (neat) 3675, 3669, 3648, 3629, 3360, 2967, 1734, 1717, 1653, 1539, 1507, 1499, 1474, 1466, 1458, 1389, 1366, 1310, 1246, 1159 $cm^{-1}$; $^1H$ NMR δ 5.01 (d, 1 H, $J$ = 7.1 Hz), 4.27-4.11 (m, 3 H), 2.62-2.55 (m, 2 H), 2.09-2.05 (m, 1 H), 1.98-1.79 (m, 2 H), 1.39 (2s, 9 H), 1.31 (s, 3 H), 0.92 (d, 3 H, $J$ = 6.4 Hz), 0.84 (d, 3 H, $J$ = 6.9 Hz); $^{13}C$ NMR δ 172.3, 155.7, 79.7, 61.6, 58.6, 54.8, 53.6, 35.5, 31.2, 28.3, 21.2, 19.1, 17.5; MS (EI) *m/z* (relative intensity) 258 ([$M-C_3H_7$]$^+$, 1), 228(1), 215 (1), 202 (1), 186 (1), 172 (10), 116 (30), 85 (20), 72 (70), 57 (100); MS (CI) *m/z* 300 ([M+H]$^+$).

**(1*S*)-[2-Methyl-1-(5-methyl-2,7,8-trioxabicyclo[3.2.1]oct-1-yl)-propyl]-carbamic acid *tert*-butyl ester (40).** According to the general procedure except that reaction mixture was stirred for 1.5 h, epoxyester **39** (301 mg, 1.0 mmol), $Cp_2ZrCl_2$ (28.8 mg, 0.1 mmol) and $AgClO_4$ (4 mg, 0.02 mmol) afforded **40** (305 mg, 96%) as an inseparable oily mixture of diastereomers: IR (neat) 3669, 3640, 3459, 2967, 2886, 1717, 1653, 1647, 1503, 1472, 1366, 1308, 1237, 1173, 1075, 1053, 1021, 999, 924, 889 $cm^{-1}$; $^1H$ NMR δ 4.71, 4.64 (2d, 1 H, $J$ = 10.8, 10.9 Hz), 4.05-3.95 (m, 2 H), 3.86-3.80 (m, 2 H), 3.50-3.35 (m, 1 H), 2.11-1.96 (m, 2 H), 1.41 (s, 10 H), 1.32, 1.20 (2s, 3 H), 0.90 (d, 3 H, $J$ = 6.9 Hz), 0.84 (d, 3 H, $J$ = 6.7 Hz); $^{13}C$ NMR δ 156.4, 120.2, 120.1, 79.1, 78.9, 78.4, 73.9, 73.3, 59.3, 59.1, 57.5, 57.4, 33.9, 33.8, 28.4, 28.0, 27.9, 22.0, 21.0, 16.9, 16.6 ; MS (EI) *m/z* (relative intensity) 301 ($M^+$, 1), 258 (7), 228 (2) 214 (2), 200 (8), 158 (20), 116 (20), 98 (10), 85 (50), 72 (50), 57 (100), 49 (40); HRMS (EI) calc. for $C_{12}H_{20}NO_5$ ($M-C_3H_7$) 258.1341, found 258.1312.

**(2*S*)-Pyrrolidine-1,2-dicarboxylic acid 1-*tert*-butyl ester 2-[2-(2-methyl-oxiranyl)-ethyl] ester (41).** According to the procedure used for **33**, Boc-L-Pro-OH (173 mg, 0.80 mmol), DCC (196 mg, 0.95 mmol), DMAP (4.9 mg, 0.04 mmol) and 3,4-epoxy-3-methylbutanol (97.5 mg, 0.95 mmol) afforded **41** (207 mg, 86%) as an inseparable oily mixture of diastereomers: IR (neat) 3650, 2975, 1750, 1701, 1653, 1647, 1507, 1478, 1458, 1397, 1366, 1256, 1165, 1123, 1088, 1034, 999, 976, 918, 774 $cm^{-1}$; $^1H$ NMR δ 4.26-4.09 (m, 3 H), 3.52-3.31 (m, 2 H), 2.59, 2.54 (AB, 2 H, $J$ = 4.7 Hz), 2.21-2.10 (m, 1 H), 1.93-1.77 (m, 5 H), 1.40, 1.35 (2s, 9 H), 1.30 (s, 3 H); $^{13}C$ NMR δ 173.0, 172.8, 154.3, 153.7, 79.8, 79.7, 61.3, 59.1, 58.8, 54.9, 54.8, 54.7, 53.5, 46.5, 46.3, 35.6, 35.5, 30.8, 29.8, 28.4, 28.3, 24.3, 23.6, 21.2; MS (EI) *m/z* (relative intensity) 243 ([$M-C_4H_8$]$^+$, 3), 226 (3), 215 (1), 198

(8), 170 (30), 114 (100), 70 (40), 57 (30); HRMS (EI) calcd. for $C_{11}H_{17}NO_5$ (M - $C_4H_8$) 243.1137, found 243.1107.

**(2*S*)-2-(5-Methyl-2,7,8-trioxabicyclo[3.2.1]oct-1-yl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester (42).** According to the general procedure except that reaction mixture was stirred for 2 h, epoxyester **41** (300 mg, 1.0 mmol), $Cp_2ZrCl_2$ (28.8 mg, 0.1 mmol), and $AgClO_4$ (4 mg, 0.02 mmol) afforded **42** (270 mg, 90%) as an inseparable oily mixture of diastereomers: IR (neat) 3650, 2975, 2888, 1690, 1653, 1647, 1456, 1404, 1364, 1296, 1262, 1175, 1146, 1111, 1055, 1022, 994, 976, 907, 764 $cm^{-1}$; $^1H$ NMR δ 4.20 (bs, 1 H), 4.07-3.94 (m, 2 H), 3.84 (dd, 1 H, $J$ = 11.3, 6.7 Hz), 3.44-3.41 (m, 2 H), 3.36-3.28 (m, 1 H), 2.05-1.94 (m, 3 H), 1.86-1.74 (m, 2 H), 1.44-1.38 (m, 10 H), 1.33 (s, 3 H); $^{13}C$ NMR δ 155.0, 121.1, 120.8, 78.8, 78.3, 73.7, 73.4, 59.0, 58.7, 58.4, 46.6, 33.7, 33.6, 28.2, 26.6, 23.2, 21.9; MS (EI) *m/z* (relative intensity) 299 ($M^+$, 2), 243 (6), 226 (6), 213 (4), 198 (10), 182 (2), 170 (10), 160 (2),114 (100), 85 (20) 68 (20), 57 (100); HRMS (EI) calc. for $C_{15}H_{25}NO_5$ 299.1733, found 299.1776.

**(2*S*)-2-Benzyloxycarbonylamino-succinic acid-4-methyl ester 1-[2-(2-methyl-oxiranyl)-ethyl]ester (44).** To a solution of 8.5 g (31.7 mmol) of Cbz-L-Asp-OH in 80 mL of DMF was added at 22 °C 7.0 g (69.7 mmol) of powdered $KHCO_3$, and 9.9 g (69.7 mmol) of iodomethane. The reaction mixture was stirred at 22 °C for 12 h, diluted with $H_2O$, and extracted with $Et_2O$ (3x). The combined ether layers were washed with $H_2O$ and brine, dried ($Na_2SO_4$), and concentrated *in vacuo*. The residue was purified by chromatography on $SiO_2$ (EtOAc/hexanes, 1 : 2) to give 8.3 g (89%) of (2*S*)-2-benzyloxycarbonylamino-succinic acid dimethyl ester as a colorless oil: $[\alpha]_D$ +29.0 (*c* 1.00, $CHCl_3$), lit.[35]: $[\alpha]_D$ +29.4 (*c* 1.00, $CHCl_3$); $^1H$ NMR δ 7.35 (bs, 5 H), 5.84 (bd, 1 H, $J$ = 8.4 Hz), 5.12 (s, 2 H), 4.67-4.62 (m, 1 H), 3.75 (s, 3 H), 3.67 (s, 3 H), 3.03 (dd, 1 H, $J$ = 17.2, 4.6 Hz), 2.85 (dd, 1 H, $J$ = 17.1, 4.5 Hz).

To a solution of 8.2 g (27.7 mmol) of (2*S*)-2-benzyloxycarbonylamino-succinic acid dimethyl ester in 80 mL of THF at 0 °C was added a solution of 1.1 g (27.2 mmol) of $LiOH•H_2O$ in 25 mL of $H_2O$. The reaction mixture was stirred at 0 °C for 2 h, treated with a solution of 2.8 g (27.7 mmol) of $KHCO_3$ in 120 mL of $H_2O$, and washed with $Et_2O$ (3x). The basic aqueous layer was acidified with 3N HCl to pH 4 and crude acid was extracted with EtOAc (3x). The combined organic layers were washed with $H_2O$ and brine, dried ($Na_2SO_4$), and concentrated *in vacuo*. The residue was purified by chromatography on $SiO_2$ (EtOAc/hexanes, 1 : 1) to give 7.1 g (91%) of **43** as a colorless oil: $[\alpha]_D$ +36.3 (*c* 0.40, $CHCl_3$); IR (neat) 3711, 3298, 1714, 1500, 1439, 1207, 1049, 736, 690 $cm^{-1}$; $^1H$ NMR δ 9.76 (bs, 1 H), 7.35 (bs, 5 H), 5.92 (bd, 1 H, $J$ = 8.3 Hz), 5.13 (s, 2 H), 4.71-4.68 (m, 1 H), 3.68 (s, 3 H), 3.07 (dd, 1 H, $J$ = 17.4, 4.3 Hz), 2.89 (dd, 1 H, $J$ = 17.1, 4.3 Hz); $^{13}C$ NMR δ 175.5, 171.7, 156.4, 136.1, 128.7, 128.4, 128.3, 67.5, 52.4, 50.3, 36.4; MS (EI) *m/z* (rel int) 281 ($M^+$, 1), 192 (1), 146 (5), 129 (7), 108 (20), 91 (100); HRMS *m/z* calcd. for $C_{13}H_{15}NO_6$ 281.0899, found 281.0909.

To a solution of 4.9 g (23.9 mmol) of DCC, 122 mg (1.0 mmol) of DMAP and 2.1 g (23.9 mmol) of 3-methyl-3-buten-1-ol in 50 mL of $CH_2Cl_2$ was added at 0 °C a solution of 5.6 g (19.9 mmol) of **43** in 50 mL of $CH_2Cl_2$. The reaction mixture was allowed to warm up to 22 °C, stirred for 12 h, filtered, and concentrated *in vacuo*. The residue was dissolved in $Et_2O$ and the solution was washed with 1% $NH_4Cl$ solution, 5% $NaHCO_3$ solution, $H_2O$ and brine, dried ($Na_2SO_4$), and concentrated *in vacuo*. The residue was purified by chromatography on $SiO_2$ (EtOAc/hexanes, 1 : 4) to give 5.0 g (71%) of (2*S*)-2-benzyloxycarbonylamino-succinic acid-4-methyl ester 1-(3-methyl-but-3-enyl)ester as a colorless oil: $[\alpha]_D$ +15.1 (*c* 1.13, $CHCl_3$); IR (neat) 3356, 2949, 1724, 1510, 1500, 1448, 1333, 1207, 1043, 893, 738, 696 $cm^{-1}$; $^1H$ NMR δ 7.35 (bs, 5 H), 5.79 (bd, 1 H, $J$ = 8.2 Hz), 5.12 (s, 2 H), 4.80 (s, 1 H), 4.72 (s, 1 H), 4.65-4.60 (m, 1 H), 4.31-4.18 (m, 2 H), 3.67 (s, 3 H), 3.02 (dd, 1 H, $J$ = 17.1, 4.3

Hz), 2.85 (dd, 1 H, $J$ = 17.1, 4.3 Hz), 2.34 (t, 2 H, $J$ = 6.6 Hz), 1.74 (s, 3 H); $^{13}$C NMR ($CD_3OD$) δ 172.5, 158.4, 143.1, 138.2, 129.6, 129.2, 129.0, 113.1, 67.9, 64.9, 52.6, 52.2, 37.6, 37.2, 22.7; MS (EI) *m/z* (rel int) 349 ($M^+$, 1), 281 (0.5), 236 (3), 214(1), 192 (13), 107 (12), 91 (100); HRMS *m/z* calcd. for $C_{18}H_{23}NO_6$ 349.1525, found 349.1538.

To a solution of 4.9 g (14.0 mmol) of (2*S*)-2-benzyloxycarbonylamino-succinic acid-4-methyl ester 1-(3-methyl-but-3-enyl)ester in 50 mL of $CH_2Cl_2$ was added at 0 °C a solution of 4.2 g (14.0 mmol) of MCPBA in 50 mL of $CH_2Cl_2$. The resulting mixture was stirred at 0 °C for 4 h, filtered, washed with 5% NaOH solution, $H_2O$ and brine, dried ($Na_2SO_4$), and concentrated *in vacuo*. The residue was purified by chromatography on $SiO_2$ (EtOAc/hexanes, 1 : 2) to give 4.6 g (89%) of **44** as a colorless oily mixture of diastereomers: IR (neat) 3655, 3314, 2934, 1709, 1502, 1425, 1201, 1041, 893, 767, 735, 690 cm$^{-1}$; $^1$H NMR δ 7.35 (bs, 5 H), 5.84 (bd, 1 H, $J$ = 8.5 Hz), 5.10 (s, 2 H), 4.63 (ddd, 1 H, $J$ = 17.2, 8.2, 4.5 Hz), 4.28-4.21 (m, 2 H), 3.66 (s, 3 H), 3.01 (dd, 1 H, $J$ = 17.1, 3.0 Hz), 2.84 (dd, 1 H, $J$ = 17.1, 4.6Hz), 2.61-2.54 (m, 2 H), 1.95-1.79 (m, 2 H), 1.31 (s, 3 H); $^{13}$C NMR δ 171.4, 170.7, 156.0, 136.2, 128.6, 128.3, 128.2, 67.2, 62.4, 54.8, 53.6, 52.1, 50.5, 36.4, 35.4, 21.1; MS (EI) *m/z* (rel int) 365 ($M^+$, 0.5), 306 (0.5), 281 (1), 263 (0.5), 236 (10), 192 (25), 108 (25), 91 (100); HRMS *m/z* calcd. for $C_{18}H_{23}NO_7$ 365.1475, found 365.1463.

**(3*S*)-3-Benzyloxycarbonylamino-3-(5-methyl-2,7,8-trioxa-bicyclo[3.2.1]oct-1-yl)-propionic acid methyl ester (45).** A solution of 2.1 g (5.8 mmol) of ester **44** in 25 mL of $CH_2Cl_2$ was treated at 22 °C with 168 mg (0.58 mmol) of $Cp_2ZrCl_2$ and 60 mg (0.29 mmol) of $AgClO_4$. The reaction mixture was stirred at 22 °C for 1 h, quenched with saturated aqueous $NaHCO_3$ solution, and extracted with EtOAc (3x). The combined organic layers were washed with $H_2O$ and brine, dried ($Na_2SO_4$), and concentrated *in vacuo*. The residue was purified by chromatography on $SiO_2$ (EtOAc/hexanes, 1 : 2) to give 2.1 g (99%) of **45** as a colorless oil: IR (neat) 3316, 2918, 1699, 1489, 1415, 1215, 1128, 1039, 733, 688 cm$^{-1}$; $^1$H NMR δ 7.36-7.33 (m, 5 H), 5.24 (bd, 1 H, $J$ = 8.0 Hz), 5.17 (s, 2 H), 4.52-4.47 (m, 1 H), 4.09-4.01 (m, 2 H), 3.91-3.85 (m, 1 H), 3.66 (s, 3 H), 3.49 (dd, 1 H, $J$ = 9.1, 7.2 Hz), 2.75-2.69 (m, 1 H), 2.59-2.51 (m, 1 H), 2.07-1.99 (m, 1 H), 1.45 (dd, 1 H, $J$ = 13.4, 4.1 Hz), 1.35 (2s, 3 H, $J$ = 3.5 Hz); $^{13}$C NMR ($CD_3OD$) δ 173.3, 158.6, 138.5, 129.5, 129.0, 128.8, 120.5, 80.9, 75.1, 74.9, 67.5, 60.7, 52.9, 52.3, 36.5, 34.8, 22.1; MS (EI) *m/z* (rel int) 365 ($M^+$, 8), 192 (10), 146 (10), 107 (23), 91 (100); HRMS *m/z* calcd. for $C_{18}H_{23}NO_7$ 365.1475, found 365.1487.

**(3*S*)-(5,5-Dimethyl-2-oxo-tetrahydro-furan-3-yl)-carbamic acid benzyl ester (46).** A solution of ortho ester **45** (40 mg, 0.11 mmol) in 2 mL of THF was treated at 0 °C with $CH_3MgBr$ (3 M in $Et_2O$, 0.2 mL, 0.6 mmol). The reaction mixture was stirred for 3 h at 0 °C and for 2 h at 10 °C, quenched by addition of $NH_4Cl$ solution, and extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with $H_2O$ (2 x 30 mL) and saturated NaCl solution (1 x 50 mL), dried ($Na_2SO_4$) and concentrated *in vacuo* to give a crude alcohol (37 mg, 92%) which was used without further purification.

A solution of this alcohol (37 mg, 0.1 mmol) in 3 mL of THF was treated at 0 °C with 0.6 mL of 1N HCl. The reaction mixture was stirred for 6 min at 0 °C and then a solution of LiOH (96 mg, 4.0 mmol) in 0.5 mL of $H_2O$ was added. The reaction mixture was stirred for 3 h at 0 °C, acidified with 1 N HCl, and extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with $H_2O$ (2 x 30 mL) and saturated NaCl solution (1 x 50 mL), dried ($Na_2SO_4$), and purified by column chromatography on $SiO_2$ (EtOAc/hexanes, 1 : 3) to give **46** (15 mg, 52%) as an oil: IR (neat) 3339, 1777, 1715, 1682, 1538, 1530, 1505, 1462, 1455, 1377, 1308, 1252, 1177, 1156, 1111, 1055, 992, 924, 741, 698 cm$^{-1}$; $^1$H NMR δ 7.32 (s, 5 H), 5.33 (d, 1 H, $J$ = 3.1 Hz), 5.12 (s, 2 H), 4.60 (ddd, 1 H, $J$ = 3.1, 8.8, 12.2 Hz), 2.67 (dd, 1 H, $J$ = 12.2, 8.8 Hz), 1.99 (t, 1 H, $J$ = 12.2 Hz), 1.50 (s, 3 H), 1.43 (s,

3 H); $^{13}C$ NMR δ 174.3, 156.1, 135.9, 128.6, 128.4, 128.2, 82.7, 67.4, 51.7, 42.4, 29.0, 27.0; MS (EI) *m/z* (relative intensity) 263 ($M^+$, 5), 158 (7), 132 (16), 112 (7), 107 (40), 96 (22), 91 (100), 84 (10), 79 (32), 68 (28), 174 (6), 156 (3), 146 (8), 115 (3), 108 (20), 91 (100), 71 (12), 57 (10); HRMS (EI) calc. for $C_{14}H_{17}NO_4$ 263.1158, found 263.1169.

**(1*S*)-[1-(5-Methyl-2,7,8-trioxa-bicyclo[3.2.1]oct-1-yl)-allyl]-carbamic acid benzyl ester (47).** A mixture of 3.2 g (8.7 mmol) of ortho ester **45**, 285 mg (13.1 mmol) of $LiBH_4$ and 530 μL (13.1 mmol) of MeOH in 60 mL of $Et_2O$ was heated at reflux for 15 min. The reaction mixture was quenched with $H_2O$ and extracted with $Et_2O$ (3x). The combined organic layers were washed with $H_2O$ and brine, dried ($Na_2SO_4$), and concentrated *in vacuo*. The residue was purified by chromatography on $SiO_2$ (EtOAc/hexanes, 1 : 1) to give 2.4 g (82%) of (1*S*)-[3-hydroxy-1-(5-methyl-2,7,8-trioxa-bicyclo[3.2.1]oct-1-yl)-propyl]-carbamic acid benzyl ester as a colorless oil that was used without further purification.

A solution of 100 mg (0.30 mmol) of this alcohol in 5 mL of THF was treated at 0 °C with 135 mg (0.59 mmol) of 2-nitrophenyl selenocyanate and 120 mg (0.59 mmol) of tri-*n*-butylphosphine. After 15 min, the reaction mixture was diluted with 20 mL of EtOAc. The organic layer was washed with brine, dried ($Na_2SO_4$), and concentrated *in vacuo*. The residue was purified by chromatography on $SiO_2$ (EtOAc/hexanes, 2 : 1), dissolved in 10 mL of THF and 4 mL of 30% $H_2O_2$ solution, and stirred at 22 °C for 6 h. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ solution and extracted with EtOAc (3x). The combined organic layers were washed with brine, dried ($Na_2SO_4$), and concentrated *in vacuo*. The residue was purified by chromatography on $SiO_2$ (EtOAc/hexanes, 2 : 1) to give 67 mg (71%) of **47** as a colorless oily mixture of diastereomers: IR (neat) 3341, 2949, 1713, 1516, 1502, 1452, 1334, 1221, 995, 696 $cm^{-1}$; $^1H$ NMR δ 7.37 (bs, 5 H), 6.02-5.91 (m, 1 H), 5.33 (d, 1 H, *J* =17.4 Hz), 5.25 (d, 1 H, *J*=10.4 Hz), 5.17 (s, 2 H), 4.62-4.52 (m, 1 H), 4.12-4.03 (m, 2 H), 3.94-3.88 (m, 1 H), 3.55-3-51 (m, 1H), 2.09-2.03 (m, 1 H), 1.46 (dd, 1 H, *J* =13.4, 4.1 Hz), 1.38 (s, 3 H); $^{13}C$ NMR δ 156.2, 136.7, 133.4, 128.7, 128.3, 119.3, 117.2, 117.0, 79.5, 74.3, 74.2, 67.1, 59.7, 56.7, 34.0, 22.0; MS (EI) *m/z* (rel int) 319 ($M^+$, 4), 228 (2), 190 (7), 146 (6), 107 (10), 91 (100); HRMS *m/z* calcd. for $C_{17}H_{21}NO_5$ 319.1420, found 319.1426.

**(2*S*)-2-Benzyloxycarbonylamino-but-3-enoic acid methyl ester (48).** A solution of 67 mg (0.21 mmol) of **47** in 5 mL of MeOH was treated with dry HCl at 0 °C until the solvent was saturated with HCl. The resulting mixture was stirred at 22 °C for 3 h and concentrated *in vacuo*. The residue was dissolved in $Et_2O$. The organic layer was washed with $H_2O$ and brine, dried ($Na_2SO_4$), and concentrated *in vacuo*. The residue was purified by chromatography on $SiO_2$ (EtOAc/hexanes, 1 : 4) to give 43 mg (82%) of **48** as a colorless oil: $[\alpha]_D$ -11.5 (*c* 0.26, MeOH), lit.[21] $[\alpha]_D$ -11.3 (*c* 0.5, MeOH); $^1H$ NMR δ 7.35 (bs, 5 H), 5.97-5.86 (m, 1 H), 5.46 (bs, 1 H), 5.37 (dd, 1 H, *J* = 17.1, 1.5 Hz), 5.29 (dd, 1 H, *J* =10.3, 1.5 Hz), 5.14 (s, 1 H), 5.0-4.9 (bs, 1 H), 3.78 (s, 3 H); $^{13}C$ NMR δ 171.1, 155.7, 136.3, 132.5, 128.8, 128.4, 118.0, 67.4, 56.3, 53.0.

**(2*S*)-2-(tert-Butyldiphenylsilanyloxy)propionic acid 2-[(2*S*)-2-methyloxiranyl]ethyl ester (50).** A solution of 0.7 g (2.1 mmol) of (2*S*)-2-(tert-butyldiphenylsilanyloxy)propionic acid (**26**) in 20 mL of dry $CH_2Cl_2$ was treated at 22 °C with 0.33 g (2.1 mmol) of 2-[(4*S*)-2,2,4-trimethyl-1,3-dioxolan-4-yl]ethanol,[36] 0.3 g (2.5 mmol) of 4-dimethylaminopyridine and 0.33 g (2.1 mmol) of 4-dimethylaminopyridine hydrochloride. The solution was stirred at 22 °C for 30 min and 0.43 g (2.1 mmol) of 1,3-dicyclohexylcarbodiimide was added. The reaction mixture was stirred at 22 °C for 20 h, filtered through a pad of celite and concentrated *in vacuo*. The residue was diluted with $Et_2O$ and filtered again. The filtrate was concentrated and chromatographed on $SiO_2$ (EtOAc/hexanes, 1:10) to give 0.68 g (69%) of (2*S*)-2-(tert-butyldiphenylsilanyloxy)propionic acid 2-[(4*S*)-2,2,4-trimethyl-1,3-

dioxolan-4-yl]ethyl ester as a colorless oil: $[\alpha]_D$ -40.4 (*c* 0.9, $CHCl_3$); IR (neat) 2960, 2860, 1754, 1113, 1060, 703 $cm^{-1}$; $^1H$ NMR δ 7.69-7.63 (m, 4 H), 7.43-7.35 (m, 6 H), 4.25 (q, 1 H, *J* = 6.7 Hz), 4.11-4.03 (m, 2 H), 3.75 (d, 1 H, *J* = 8.6 Hz), 3.63 (d, 1 H, *J* = 8.5 Hz), 1.79-1.74 (m, 2 H), 1.35 (d, 3 H, *J* = 6.7 Hz), 1.34 (s, 6 H), 1.23 (s, 3 H), 1.09 (s, 9 H); $^{13}C$ NMR δ 173.7, 136.0, 135.8, 133.5, 133.2, 129.9, 127.7, 109.3, 79.6, 74.2, 69.0, 61.3, 38.2, 27.1, 26.9, 25.0, 21.4, 19.3; MS (EI) *m/z* (relative intensity) 455 ($[M-CH_3]^+$, 35), 413 (15), 355 (20), 283 (95), 271 (35), 199 (100), 181 (40), 143 (55), 115 (80), 105 (20); HRMS (EI) *m/z* calcd. for $C_{26}H_{25}O_5Si$ ($M-CH_3$): 455.2254, found: 455.2265.

A solution of (2*S*)-2-(tert-butyldiphenylsilanyloxy)propionic acid 2-[(4*S*)-2,2,4-trimethyl-1,3-dioxolan-4-yl]ethyl ester (400 mg, 0.85 mmol) in a mixture of THF (4 mL) and 0.9 M aqueous $H_2SO_4$ (4 mL) was stirred at 50 °C for 4h. After neutralization with 1 M aqueous NaOH, extraction with $Et_2O$ (3x) and chromatography on $SiO_2$ (EtOAc/hexanes, 1:1) afforded 190 mg (52%) of (2*S*)-2-(tert-butyldiphenylsilanyloxy)propionic acid (3*S*)-3,4-dihydroxy-3-methylbutyl ester as a colorless oil: $[\alpha]_D$ -39.5 (*c* 1.5, $CHCl_3$); IR (neat) 3426, 2930, 1726, 1423, 1132, 972, 736, 700 $cm^{-1}$; $^1H$ NMR δ 7.68-7.63 (m, 4 H), 7.45-7.34 (m, 6 H), 4.27 (q, 1 H, *J* = 6.7 Hz), 4.18-4.08 (m, 2 H), 3.39-3.37 (m, 2 H), 2.19-2.05 (m, 2 H), 1.80-1.65 (m, 2 H), 1.35 (d, 3 H, *J* = 6.7 Hz), 1.14 (s, 3 H), 1.09 (s, 9 H); $^{13}C$ NMR δ 173.7, 135.9, 135.8, 133.4, 133.2, 129.9, 127.7, 71.9, 69.9, 69.1, 61.2, 36.8, 26.9, 23.7, 21.4, 19.3; MS (EI) *m/z* (relative intensity) 373 ($[M-C_4H_9]^+$, 2), 321 (55), 271 (80), 139 (35), 85 (80), 71 (15); HRMS (EI) *m/z* calcd. for $C_{20}H_{25}O_5Si$ ($M-C_4H_9$): 373.1471, found: 373.1482.

A solution of (2*S*)-2-(tert-butyldiphenylsilanyloxy)propionic acid (3*S*)-3,4-dihydroxy-3-methylbutyl ester (80 mg, 0.185 mmol) and triethylamine (31 µL, 0.22 mmol) in 1 mL of $CH_2Cl_2$ was treated at -10 °C with methanesulfonyl chloride (14 µL, 0.185 mmol). After 15 min, the reaction mixture was diluted with $Et_2O$ and washed successively with ice-cold water, cold 1 M aqueous HCl solution, saturated aqueous $NaHCO_3$ solution and brine. The organic phase was dried ($Na_2SO_4$) and concentrated. Chromatography of the residue on $SiO_2$ (EtOAc/hexanes, 1:3) gave 92 mg (98%) of (2*S*)-2-(tert-butyldiphenylsilanyloxy)propionic acid (3*S*)-3-hydroxy-4-methanesulfonyloxy-3-methylbutyl ester as a colorless oil: $[\alpha]_D$ -34.4 (*c* 0.66, $CHCl_3$); IR (neat) 3495, 2930, 1724, 1344, 1128, 1055, 964, 700 $cm^{-1}$; $^1H$ NMR δ 7.68-7.63 (m, 4 H), 7.44-7.36 (m, 6 H), 4.27 (q, 1 H, *J* = 6.7 Hz), 4.16-4.11 (m, 2 H), 4.04-3.95 (m, 2 H), 3.04 (s, 3 H), 2.31 (s, 1 H), 1.81-1.68 (m, 2 H), 1.36 (d, 3 H, *J* = 6.8 Hz), 1.22 (s, 3 H), 1.09 (s, 9 H); $^{13}C$ NMR δ 173.6, 135.9, 135.8, 133.3, 133.1, 129.9, 127.7, 75.8, 70.6, 69.0, 60.5, 37.5, 36.5, 26.9, 23.8, 21.3, 19.3; MS (EI) *m/z* (relative intensity) 451 ($[M-C_4H_9]^+$, 12), 349 (10), 283 (35), 271 (45), 199 (95), 181 (40), 85 (100); HRMS (EI) *m/z* calcd. for $C_{21}H_{27}O_7SiS$ ($M-C_4H_9$): 451.1247, found: 451.1246.

A solution of (2*S*)-2-(tert-butyldiphenylsilanyloxy)propionic acid (3*S*)-3-hydroxy-4-methanesulfonyloxy-3-methylbutyl ester (60 mg, 0.12 mmol) in 0.5 mL of $CH_2Cl_2$ was treated at 22 °C with a solution of 20 mg (0.12 mmol) of 1,8-diazabicyclo[5.4.0]undec-7-ene in 0.5 mL of $CH_2Cl_2$. The reaction mixture was stirred at 22 °C for 10 min, diluted with $Et_2O$, washed with cold 1 M aqueous HCl solution, saturated aqueous $NaHCO_3$ solution, and brine, and dried ($Na_2SO_4$). The solution was concentrated and chromatographed on florisil (EtOAc/hexanes, 1:10) to give 42 mg (86%) of **50** as a colorless oil: $[\alpha]_D$ -31.8 (*c* 2.1, $CHCl_3$); IR (neat) 2934, 1745, 1186, 1132, 970, 700 $cm^{-1}$; $^1H$ NMR δ 7.69-7.64 (m, 4 H), 7.46-7.33 (m, 6 H), 4.27 (q, 1 H, *J* = 6.7 Hz), 4.13-3.97 (m, 2 H), 2.56 (d, 1 H, *J* = 4.8 Hz), 2.51 (d, 1 H, *J* = 4.8 Hz), 1.88-1.66 (m, 2 H), 1.37 (d, 3 H, *J* = 6.7 Hz), 1.28 (s, 3 H), 1.09 (s, 9 H); $^{13}C$ NMR δ 173.6, 135.9, 135.8, 133.5, 133.2, 129.9, 127.7, 127.6, 68.9, 61.1, 54.8, 53.6, 35.4, 26.9, 21.3, 19.3; MS (EI) *m/z* (relative intensity) 355 ($[M-C_4H_9]^+$, 30), 325 (30), 283 (60), 199 (55), 175 (25), 85 (100); HRMS (EI) *m/z* calcd. for $C_{20}H_{23}O_4Si$ ($M-C_4H_9$): 355.1366, found: 355.1364.

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## References and Notes

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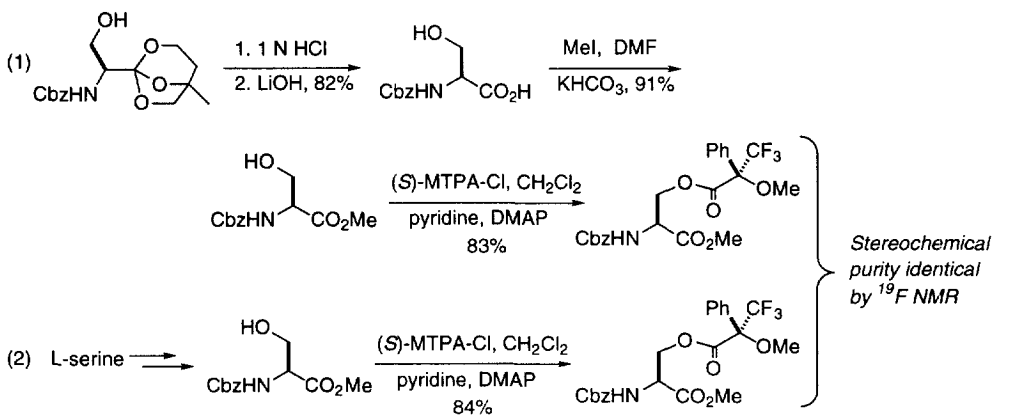


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