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Stereoselective synthesis of constrained oxacyclic hydroxyethylene isosteres of aspartyl protease inhibitors. Nitroaldol methodology toward 2,3-substituted tetrahydrofurans☆

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Dedicated to Dieter Seebach, chemist extraordinaire, scholar and friend

Abstract—The Shibasaki heterobimetallic Binol lanthanide, and Trost dinuclear zinc catalysts were studied in a nitroaldol reaction of 3-methyl-1-nitrobutane with a chiral non-racemic tetrahydrofuran aldehyde. Other methods utilized KF, Amberlyst A-21, and *t*-BuOK as bases for the same nitroaldol reaction. The major isomer in the Binol lanthanide and dinuclear zinc catalyzed reactions was the *syn/syn*-nitroaldol product. Structures were confirmed by single-crystal X-ray crystallography. The major nitroaldol isomer was converted to a 2,3-substituted tetrahydrofuran 2-carboxylic acid containing a γ,δ-amino alcohol branch, corresponding to a constrained oxacyclic analogue of a hydroxyethylene isostere of aspartyl protease inhibitors.

1. Introduction

The synthesis of functionalized tetrahydrofurans has been an area of long-standing interest in conjunction with natural product synthesis harboring such motifs.[1] Numerous methods have been reported covering a wide range of strategies, depending on the pattern, and nature of the substituents on the tetrahydrofuran ring. An obvious choice in some instances has been to manipulate the appropriate furanoid sugar,[2] or the elaboration of γ-butyrolactones.[3] Asymmetric methods of synthesis under catalytic or non-catalytic conditions have also been reported.[4]

Several synthetic inhibitors of aspartyl proteases include a hydroxyethylene isostere subunit corresponding to a 2-alkyl-4-hydroxy-5-amino-1-carboxylic acid or to the truncated statine-type variant[5] (Fig. 1A). We envisaged an oxacyclic, conformationally constrained variant of an acyclic hydroxyethylene isostere in which the requisite functional groups had the correct absolute configurations for

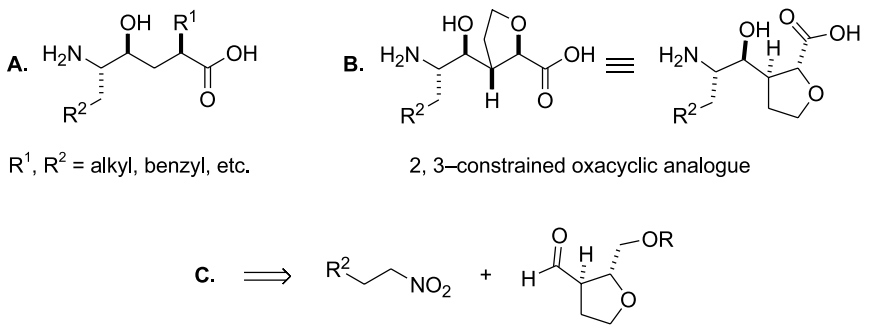

Figure 1. Oxacyclic hydroxyethylene peptide isostere core subunits.

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effective interactions with aspartyl residues of a given enzyme.[5] In essence, the space encompassed by the C-2 alkyl group and the adjacent methylene in the acyclic chain, could be occupied by the five membered oxacycle as depicted in perspective drawings in Figure 1B. Consideration of various approaches to such a motif having four contiguous stereogenic centers, led us to explore the nitroaldol reaction between suitable 1-nitroalkanes and a 3-aldehydo-2-hydroxymethyl tetrahydrofuran of known absolute configuration (Fig. 1C).

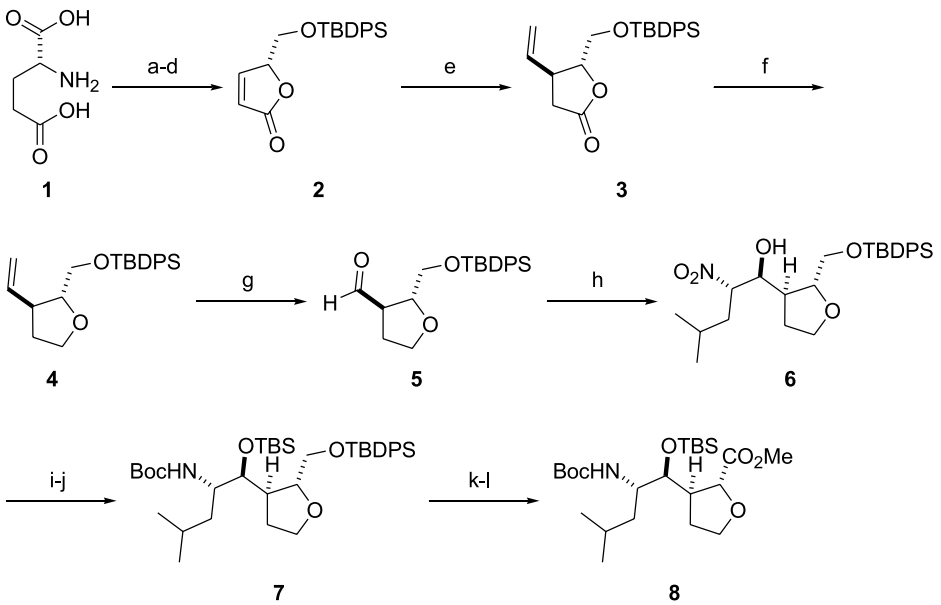
The venerable nitroaldol (Henry) reaction[6] has been a classical method for the synthesis of α-hydroxy nitroalkanes for over a century.[7] Important applications can be found, in the synthesis of natural products and medicinally important compounds.[7] α-Hydroxy nitroalkanes are easily converted to α-hydroxy aldehydes (Nef reaction),[8] nitroolefins, α-amino alcohols and related functionalities. In the original report, Henry described the reaction of nitromethane with acetaldehyde to give 1-nitro-2-hydroxypropane, and compared it to the cyanohydrin reaction.[6] Nearly a century later, Seebach and co-workers[9] showed that bis-lithiated nitronates and silylnitronates were excellent nucleophiles for the reaction. *Syn*- or *anti*-α-hydroxy nitroalkanes could be obtained as major or minor diastereomers depending on the quench method, the reaction conditions, and the presence of additives. In 1983, Rosini and co-workers,[10] reported the synthesis of α-hydroxy nitroalkanes in good yields simply by bringing the nitroalkane and the aldehyde in contact with chromatography-grade alumina. The method was successfully applied for the synthesis of aminodeoxy sugars.[11] Subsequently, the condensing medium was changed to the tetraalkylammonium resin Amberlyst A-21 by Ballini and co-workers[12] with improved yields of adducts. Potassium fluoride has been used as a mild base in asymmetric nitroaldol condensations of aldehydo esters of 8-phenylmenthol by Solladié-Cavallo.[13] Tetrabutylammonium fluoride was the promoter of choice in the condensation of primary nitroalkanes with α,α-*N*,*N*-dibenzylamino aldehydes.[14] Nitrogen bases such as tetramethylguanidine[15] have also found, many uses in nitroaldol reactions. Extension to chiral guanidines have been explored in diastereoselective nitroaldol reactions.[16] Condensations in the presence of catalytic amounts of proazaphosphatranes were described by Kisanga and Verkade.[17]

Recently, several groups have reported catatylic asymmetric versions of the nitroaldol reaction, especially with nitromethane. Thus, Shibasaki[18] has utilized chiral non-racemic Binol lanthanides in nitroaldol reactions with nitromethane, and extended the methodology to simple primary nitroalkanes affording *syn*-nitroaldol products with unsubstituted aldehydes.[19] Trost[20] has used a dinuclear zinc catalyst, while Jørgensen[21] and Evans[22] have exploited bis-oxazoline copper catalyst. Finally, chiral quaternary ammonium salts have been described in the catalytic asymmetric synthetis of nitroaldol reactions by Corey[23] and Maruoka,[24] respectively. With three exceptions,[19,21,24] all nitroaldol reactions were done with nitromethane, leading to enantioenriched 1-nitro-2-hydroxy adducts.

With a plethora of methods to prepare α-hydroxynitroalkanes relying on diastereoselective methods with various additives, and the possibility to extend such reactions to catalytic asymmetric variants, we embarked on the synthesis of the intended oxacyclic hydroxyethylene α-amino alcohol isostere (Fig. 1B and C).

2. Results

Our initial studies were focused on the use of 3-methyl-1-nitrobutane as the nucleophile. The requisite aldehyde



Scheme 1. Reagents and conditions: (a) $NaNO_2$, H_2SO_4, H_2O, 0 °C (55%); (b) $BH_3{\cdot}Me_2S$, THF, 0 °C (80%); (c) TBDPSiCl, Et_3N, DMAP, CH_2Cl_2 (85%); (d) 1. LiHMDS, PhSeBr, THF, −78 °C; 2. H_2O_2, CH_2Cl_2, 0 °C (60%, 2 steps); (e) CuI, $CH_2{=}CHMgBr$, Me_2S, THF, −78 °C (80%); (f) 1. DIBAL, CH_2Cl_2, −78 °C; 2. Et_3SiH, $BF_3{\cdot}Et_2O$, CH_2Cl_2, −45 °C (85%, 2 steps); (g) O_3, PPh_3, CH_2Cl_2, −78 °C (90%); (h) 3-methyl-1-nitrobutane, $LaLi_3$(R-Binol)$_3{\cdot}$LiOH, THF, −40 °C (46%, major isomer); (i) TBSOTf, 2,6-Lutidine, CH_2Cl_2 (90%); (j) 1. H_2 (5 atm), Raney-Ni, H_2PtCl_6, MeOH; 2. Boc_2O, THF/Et_3N (9:1) (90%, 2 steps); (k) TBAF/AcOH (1:1), THF, 40% (l) 1. PDC, DMF; 2. CH_2N_2, CH_2Cl_2 (57%, 2 steps).

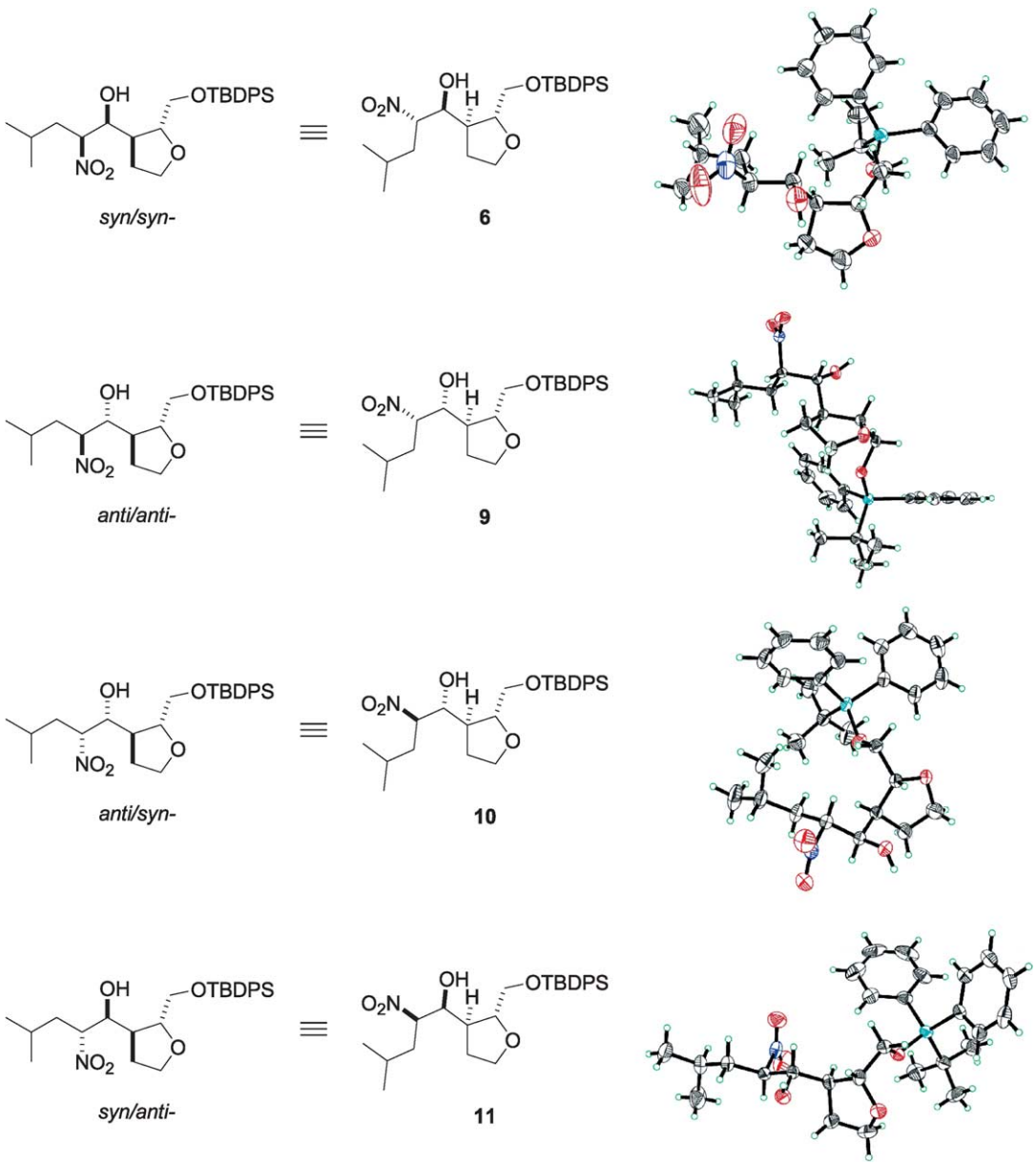


Figure 2. Ortep representations of X-ray crystal structures of nitroaldol products **6**, **9**, **10** and **11**.

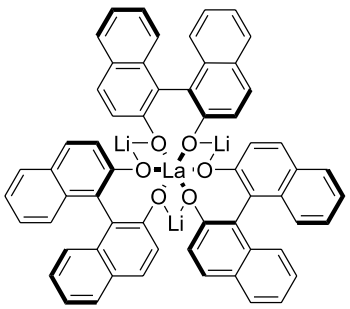
(Fig. 1C, R=TBDPS), was prepared in eight steps from *R*-glutamic acid **1** using previously developed methodology in the enantiomeric series[25] (Scheme 1). Thus, addition of a mixed vinylmagnesium cuprate to the unsaturated lactone **2** afforded the vinyl adduct **3** in excellent yield. Treatment with Dibal followed by triethylsilane and $BF_3{\cdot}Et_2O$ afforded the corresponding 3-vinyl tetrahydrofuran **4**. Finally, oxidative cleavage of the double bond by ozonolysis led to the desired aldehyde **5** in 13% yield for eight steps.

The nitroaldol reaction was first done in the presence of several promoters using 3-methyl-1-nitrobutane as a representative precursor of the amino moiety, and 3-phenylpropanal as a model aldehyde. Attempted condensation with the guanidinium nitronate or in the presence of alumina gave only starting aldehyde. Formation of the lithium nitronate with butyl lithium gave the expected mixture of nitroaldol products. Since preliminary results had shown promising selectivity with the key aldehyde **5** utilizing the Shibasaki Binol lanthanide catalyst,[18] we proceeded to optimize the reaction further utilizing the second generation catalyst.[18c] Thus, reaction at −40 °C for 80 h led to a mixture of all four diastereomers of which the desired *syn/syn*-isomer **6** was preponderant (46% isolated). The structure and absolute stereochemistry was confirmed by a single crystal X-ray structure. The structures of the other diastereomers were also confirmed by X-ray crystallographic analysis (Fig. 2). The crystalline nitroaldol products are shown in their order of elution by column chromatography. Thus, isomers **9** and **10** were followed by **11**, and the desired **6** which was the most polar. A small quantity of unreacted aldehyde **5** (10–15%) was also isolated. With the desired diastereomer **6** in hand, we proceeded with its elaboration to the intended δ-amino acid motif (Fig. 1B).

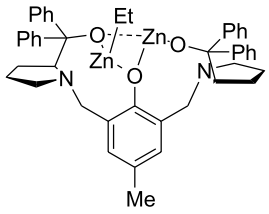
Thus, protection of the hydroxyl group as a TBS ether, reduction of the nitro group in the presence of Raney-Ni and H_2PtCl_6,[26] followed by treatment with Boc anhydride, gave

Table 1. Nitroaldol reaction conditions

Entry	Catalyst	Conditions	Yield (%)[a]	Ratio and % yield[b]			
				9	**10**	**11**	**6**
1	Amberlyst A-21	THF, rt	60	1, 10%	1.6, 17%	1.1, 12%	1.9, 20%
2	KF	*i*-PrOH, rt	52	1, 10%	1, 10%	1.3, 12%	2, 20%
3	*t*-BuOK	*t*-BuOH/THF (1:1), −25 °C	70	1.4, 13%	2, 18%	1, 9%	3.5, 30%
4	*t*-BuOLi	*t*-BuOH/THF (1:1), −25 °C	70	1, 11%	1.4, 16%	1.2, 13%	2.7, 30%
5	$LaLi_3$(*R*-Binol)$_3$·LiOH (Shibasaki)[18c]	THF, −40 °C	65[c]	1.5, 3%	5.5, 13%	1, 3%	20, 46%
6	$LaLi_3$(*S*-Binol)$_3$·LiOH (Shibasaki)	THF, −40 °C	65	2.3, 11%	5.6, 26%	1, 5%	5, 23%
7	Dinuclear Zn catalyst (Trost)[20]	THF, rt	60[c]	4.4, 15%	3.9, 14%	1, 4%	8.7, 29%



Shibasaki heterobimetallic catalyst[18]



Trost dinuclear Zn catalyst[20]

[a] Total yield of all isomers.
[b] Yield percentage of isomers based on weights of isolated products.
[c] Starting aldehyde **5** could be recovered (10–15%).

the N-Boc derivative **7** in excellent overall yield (Scheme 1). Several other reduction conditions were tried but were not satisfactory or led to decomposition (Pd/C, Raney-Ni, PtO_2, SmI_2,[27] Al–Hg,[28] $NaBH_4$, $NiCl_2$).[29] Selective desilylation and oxidation of the primary alcohol with PDC in DMF led to the corresponding carboxylic acid which was characterized as the ester **8**.

Other promoters and catalysts were also tried for the nitroaldol reaction shown in Table 1. In the presence of Amberlyst A-21 or KF, the diastereomeric ratios favoring **6** were disappointing (Table 1, entry 1,2). Some improvement could be seen in the presence of Li or *t*-BuOK as the base (Table 1, entry 3, 4). With Trost's dinuclear zinc catalyst,[20] the reaction was slow even at room temperature. However, the desired isomer **6** was formed in a 2:1:1 ratio with respect to the diastereomeric compounds **9** and **10** (Table 1). Unreacted aldehyde **5** was also recovered in this case (~15%).

With the Shibasaki *R*-Binol catalyst,[18c] the second significant diastereomer was found to be the *anti/syn*-adduct **10**, while the *anti/anti*- and *syn/anti*-isomers **9** and **11**, respectively, were formed in negligible quantities (Table 1, entry 5, Fig. 2). It is also of interest that the *S*-Binol lanthanide catalyst gave a quasi-equivalent ratio of isomers **6** and **10** (Table 1, entry 6) reflecting a mismatched pairing. The preponderance of *syn*-nitroaldol products with nitroethane and hexanal for example has been rationalized based on steric hinderance.[19] Control experiments showed that the products **6**, **9**, **10** and **11** were configurationally stable under the Shibasaki reaction conditions.

As previously mentioned the majority of intermolecular catalytic asymmetric nitroaldol reactions reported so far have utilized nitromethane and relatively simple aldehydes. The successful application of the Shibasaki catalytic reaction to higher primary nitroalkanes and an oxacyclic carbaldehyde with a bulky ether appendage such as **5**, is a useful extension that warrants further investigation. The incorporation of the oxacyclic hydroxyethylene isostere in structure-based designed potential inhibitors of aspartyl proteases will be reported in due course.

3. Experimental

3.1. General

3.1.1. (*R*)-5-(*tert*-Butyldiphenylsilanyloxymethyl)-(*S*)-4-vinyldihydrofuran-2-one (3). To a suspension of CuI (1.6 g, 8.4 mmol) in THF (40 ml) at −78 °C was added vinylmagnesium bromide (1.6 M/THF) (10.5 ml, 16.8 mmol). The mixture was stirred for 10 min, Me_2S was added, and stirring was continued at −78 °C for 2 h 30 min, after which, a solution of **2** (1.0 g, 2.8 mmol) in THF (20 ml) was added dropwise. After 2 h, reaction was quenched by adding a 1:1 mixture (100 ml) of saturated aqueous NH_4Cl solution and aqueous ammonium hydroxide. Ether was added and the resulting mixture was stirred vigorously for 1 h. The combined organic phases were washed with a 1:1 mixture of saturated aqueous NH_4Cl, aqueous ammonium hydroxide, and brine. Drying with Na_2SO_4, concentration under vacuum, and purification by flash chromatography (10% AcOEt/hexanes) gave **3**

(852 mg, 2.2 mmol, 80%); $[\alpha]_D^{20}$ −28.7° (*c* 3.1, $CHCl_3$), reported[30] $[\alpha]_D^{20}$ +33.1° (*c* 0.7, $CHCl_3$); (film) (cm^{-1}) 1794 (C=O); NMR ^1H ($CDCl_3$, 400 MHz) δ (ppm) 7.70–7.67 (m, 4H), 7.48–7.39 (m, 6H), 5.81–5.72 (ddd, *J*=8.0, 10.6, 16.7 Hz, 1H), 5.15 (s, 1H), 5.13–5.11 (d, *J*=7.1 Hz, 1H), 4.28–4.25 (td, *J*=3.3, 6.8 Hz, 1H), 3.97–3.93 (dd, *J*=2.8, 11.7 Hz, 1H), 3.76–3.72 (dd, *J*=3.4, 11.7 Hz, 1H), 3.26–3.18 (qu, *J*=8.0 Hz, 1H), 2.88–2.81 (dd, *J*=9.0, 17.6 Hz, 1H), 2.50–2.43 (dd, *J*=8.5, 17.6 Hz, 1H), 1.08 (s, 9H); NMR ^{13}C ($CDCl_3$, 100 MHz) δ (ppm) 176.5, 136.8, 136.1, 136.0, 133.3, 133.0, 130.4, 128.3, 117.9, 85.0, 63.7, 41.2, 35.5, 27.2, 19.7; HRMS: calcd 380.1808; found, 380.1751.

3.1.2. (*R*)-2-(*tert*-Butyldiphenylsilanyloxymethyl)-(*S*)-3-vinyltetrahydrofuran (4). To a solution of **3** (1.0 g, 2.6 mmol) in CH_2Cl_2 (10 ml) at −78 °C was added DIBAL (1.5 M/toluene) (2.1 ml, 31.5 mmol) dropwise. After stirring for 3 h, few drops of water were added and stirring was continued for another hour. Temperature was raised to 0 °C, ether (10 ml) and water (0.5 ml) were added and the resulting mixture was stirred 20 min at room temperature. The resulting gel was filtered through Celite and washed with hot AcOEt. After evaporation of the solvents under vacuum, the residue was dissolved in CH_2Cl_2 (10 ml) and Et_3SiH (648 mg, 3.9 mmol) was added. The resulting solution was cooled to −45 °C and $BF_3{\cdot}Et_2O$ (412 mg, 2.9 mmol) was added dropwise. After stirring for 3 h, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ and phases were separated. Drying with Na_2SO_4, concentration under vacuum, and purification by flash chromatography (5% AcOEt/hexanes) gave **4** (809 mg, 2.2 mmol, 85%);. $[\alpha]_D^{20}$ −8.7° (*c* 0.9, $CHCl_3$); IR (film) (cm^{-1}) 2932; NMR ^1H ($CDCl_3$, 400 MHz) δ (ppm) 7.78–7.75 (m, 4H), 7.49–7.40 (m, 6H), 5.83–5.74 (ddd, *J*=8.1, 10.2, 17.1 Hz, 1H), 5.10–5.05 (ddd, *J*=1.0, 1.6, 17.1 Hz, 1H), 5.05–5.02 (ddd, *J*=0.7, 1.7, 10.2 Hz, 1H), 4.01–3.71 (m, 5H), 2.88–2.80 (qu, *J*=8.0 Hz, 1H), 2.19–2.12 (m, 1H), 1.90–1.80 (m, 1H), 1.12 (s, 9H); NMR ^{13}C ($CDCl_3$, 100 MHz) δ (ppm) 138.9, 135.6, 133.5, 129.5, 127.5, 115.3, 84.0, 67.9, 64.7, 45.0, 33.2, 26.7, 19.1.

3.1.3. (*R*)-2-(*tert*-Butyldiphenylsilanyloxymethyl)-tetrahydrofuran-(*R*)-3-carbaldehyde (5). Through a solution of **4** (591 mg, 1.6 mmol) in CH_2Cl_2 (16 ml) at −78 °C was passed a stream of ozone during 30 min until a blue color persisted. The solution was stirred under argon for another 30 min and the ozonide was reduced with PPh_3 (420 mg, 1.6 mmol). The mixture was stirred for 4 h at room temperature. Evaporation under vacuum and purification by flash chromatography (5% AcOEt/hexanes) gave **5** (531 mg, 1.4 mmol, 90%); $[\alpha]_D^{20}$ −21.0° (*c* 1.25; $CHCl_3$); IR (film) (cm^{-1}) 1727.3 (C=O); NMR ^1H ($CDCl_3$, 400 MHz) δ (ppm) 9.72–9.71 (d, *J*=2.3 Hz, 1H), 7.74–7.66 (m, 4H), 7.47–7.38 (m, 6H), 4.27–4.21 (m, 1H), 3.98–3.82 (m, 2H), 3.80–3.75 (dd, *J*=4.3, 10.6 Hz, 1H), 3.74–3.69 (dd, *J*=5.5, 10.6 Hz, 1H), 3.15–3.07 (m, 1H), 2.31–2.08 (m, 2H), 1.06 (s, 9H); NMR ^{13}C ($CDCl_3$, 100 MHz) δ (ppm) 201.3, 136.0, 136.0, 133.5, 133.5, 130.3, 130.2, 128.2, 128.2, 79.7, 68.8, 65.5, 54.5, 27.6, 27.2, 19.6; MS (*m*/*z*) 291.2 (M−C_6H_5); HRMS: calcd 368.1808; found, 368.1801.

3.1.4. (*S*)-1-[(*R*)-2-(*tert*-Butyldiphenylsilanyloxymethyl)-tetrahydrofuran-(*R*)-3-yl]-4-methyl-(*S*)-2-nitropentan-1-ol (6). *Method A: heterobimetallic catalyst (Shibasaki).*[18c] The catalyst was prepared as follows: to a solution of (*R*)-(+)-1,1′-bi(2-naphthol) (100 mg, 0.35 mmol) in THF (10 ml) was added a solution of La(O*i*-Pr)$_3$ (37 mg, 116 μmol) in THF (1.5 ml) at 0 °C. To this mixture was added BuLi (2.5 M/hexanes) (140 μl). The ice bath was removed and mixture was stirred for 12 h. Water (1 M/THF) (116 μl) and BuLi (2.5 M/hexanes) (42 μl) were added and the catalyst was used as such. To a solution of catalyst (3.7 ml) at −40 °C was added 3-methyl-1-nitrobutane[31] (1.3 ml, 11 mmol) and the mixture was stirred 30 min. A solution of **5** (400 mg, 1.1 mmol) in THF (3.3 ml) was added and the reaction mixture was stirred for 80 h. The mixture was quenched with HCl 1.2 M (2 ml), the aqueous phase was extracted with ether (3×10 ml) and the organic phase was washed with brine. Drying with Na_2SO_4, concentration under vacuum, and purification by flash chromatography (1% AcOEt/CH_2Cl_2 to isolate **9** and **10** and a gradient to 5% AcOEt/CH_2Cl_2 to isolate **11** and **6**) gave the four isomers **9** (17 mg, 35 μmol, 3%), **10** (69 mg, 142 μmol, 13%), **11** (14 mg, 29 μmol, 3%) and **6** (246 mg, 507 μmol, 46%), by order of elution, respectively.

For isomer **9**, mp 84–86 °C; $[\alpha]_D^{20}$ −19.4° (*c* 0.82, $CHCl_3$); IR (film) (cm^{-1}) 3392 (OH), 1551 (NO_2); NMR ^1H ($CDCl_3$, 400 MHz) δ (ppm) 7.70–7.67 (m, 4H), 7.46–7.41 (m, 6H), 4.58–4.55 (m, 1H), 4.08–4.03 (m, 2H), 3.93–3.89 (m, 1H), 3.83–3.73 (m, 2H), 3.64–3.60 (m, 2H), 2.33–2.23 (m, 2H), 2.00–1.97 (m, 1H), 1.75–1.50 (m, 3H), 1.08 (s, 9H), 1.00–0.99 (d, *J*=6.5 Hz, 3H), 0.96–0.95 (d, *J*=6.4 Hz, 3H); NMR ^{13}C ($CDCl_3$, 100 MHz) δ (ppm) 135.5, 133.5, 132.4, 132.3, 129.8, 127.7, 89.4, 82.3, 75.5, 67.6, 66.2, 45.9, 35.5, 30.1, 26.6, 24.9, 23.2, 21.1, 19.0; MS (*m*/*z*) 486 (M+1); HRMS: calcd 485.2598; found, 485.2592.

For isomer **10**, mp 145–147 °C; $[\alpha]_D^{20}$ −10.4° (*c* 0.68, $CHCl_3$); IR (film) (cm^{-1}) 3392 (OH), 1551 (NO_2); NMR ^1H ($CDCl_3$, 400 MHz) δ (ppm) 7.71–7.65 (m,4H), 7.48–7.39 (m, 6H), 4.68–4.64 (dt, *J*=3.4, 9.9 Hz, 1H), 4.10–4.02 (m,1H), 3.93–3.88 (m,H), 3.80–3.72 (m,2H), 3.68–3.62 (m,1H), 3.55–3.51 (m, 2H), 2.34–2.22 (m, 3H), 1.71–1.61 (m, 3H), 1.07 (s, 9H), 0.98 (d, *J*=2.8 Hz, 3H), 0.96 (d, *J*=2.7 Hz, 3H); NMR ^{13}C ($CDCl_3$, 100 MHz) δ (ppm) 136.1, 136.0, 132.8, 130.4, 128.3, 89.1, 82.2, 75.6, 68.3, 66.5, 46.6, 39.3, 31.3, 27.2, 25.5, 23.1, 22.1, 19.5; MS (*m*/*z*) 486 (M+1); HRMS: calcd. 485.2598; found, 485.2589.

For isomer **11**, mp 104–107 °C; $[\alpha]_D^{20}$ −10.8° (*c* 0.98, $CHCl_3$); IR (film) (cm^{-1}) 3401 (OH), 1549 (NO_2); NMR ^1H ($CDCl_3$, 400 MHz) δ (ppm) 7.69–7.65 (m, 4H), 7.47–7.39 (m, 6H), 4.55–4.50 (ddd, *J*=2.6, 5.9, 11.5 Hz, 1H), 4.04–4.01 (m, 1H), 3.91–3.81 (m, 3H), 3.71–3.67 (dd, *J*=4.5, 10.8 Hz, 1H), 3.66–3.62 (dd, *J*=5.1, 10.8 Hz, 1H), 2.37 (m, 1H), 2.28–2.22 (m, 1H), 2.14–1.94 (m, 3H), 1.67–1.48 (m, 2H), 1.07 (s, 9H), 0.95–0.93 (d, *J*=6.5 Hz, 3H), 0.92–0.90 (d, *J*=6.4 Hz, 3H); NMR ^{13}C ($CDCl_3$, 100 MHz) δ (ppm) 136.1, 136.0, 133.6, 130.2, 130.2, 128.2, 89.9, 81.6, 73.1, 68.6, 65.9, 44.0, 38.4, 27.2, 26.6, 25.5, 23.6, 21.5, 19.6; MS (*m*/*z*) 486 (M+1); HRMS: calcd 485.2598; found, 485.2594.

For isomer **6**, mp 128–131 °C; $[\alpha]_D^{20}$ −30.6° (*c* 1.73,

$CHCl_3$); IR (film) (cm^{-1}) 3346 (OH), 1558 (NO_2); NMR ^1H ($CDCl_3$, 400 MHz) δ (ppm) 7.71–7.66 (m, 4H), 7.47–7.39 (m, 6H), 4.59–4.54 (ddd, J=3.2, 8.0, 11.2 Hz, 1H), 4.04–4.01 (dd, J=2.1, 7.7 Hz, 1H), 3.92–3.78 (m, 4H), 3.72–3.68 (dd, J=5.4, 10.7 Hz, 1H), 2.38–2.28 (m, 2H), 2.08–1.94 (m, 2H), 1.84–1.76 (m, 1H), 1.60–1.50 (m, 1H), 1.46–1.39 (m, 1H), 1.09 (s, 9H), 0.98–0.97 (d, J=6.4 Hz, 3H), 0.95–0.93 (d, J=6.6 Hz, 3H); NMR ^{13}C ($CDCl_3$, 100 MHz) δ (ppm) 136.1, 136.0, 133.6, 130.3, 130.3, 128.2, 128.2, 91.2, 81.2, 72.5, 68.6, 65.9, 43.8, 39.8, 27.3, 25.5, 25.5, 23.6, 21.5, 19.6; MS (*m*/*z*) 486 (M+1); HRMS: calcd 485.2598; found, 485.2594.

The procedure with (*S*)-(−)-1,1′-bi(2-naphthol) and **5** (37 mg, 100 μmol) was the same and gave the four isomers: **9** (5.4 mg, 11 μmol, 11%), **10** (12.8 mg, 26 μmol, 26%), **11** (2.2 mg, 5 μmol, 5%) and **6** (11.5 mg, 23 μmol, 23%).

Method B: dinuclear Zn catalyst (Trost).[20] To a solution of **5** (60 mg, 163 μmol) and 3-methyl-1-nitrobutane[31] in THF (0.5 ml) at −78 °C was added dinuclear Zn catalyst (82 μl) (0.1 M prepared as follows: Et_2Zn (1 M/hexanes) (0.4 ml) was added dropwise to a solution of the ligand precursor (synthesized in 3 steps from *p*-cresol and (*S*)-(−)-α,α-diphenyl-2-pyrrolidinemethanol)[20] (128 mg, 0.2 mmol) in THF (2 ml) at 0 °C. The ice bath was removed and the mixture was stirred 4 days. Reaction was quenched with 0.5 M HCl and the aqueous phase was extracted with ether. The organic phase was washed with water and brine, dried with Na_2SO_4, evaporated under vacuum, then purified by flash chromatography (see method A) to give the four isomers: **9** (11.6 mg, 24 μmol, 15%), **10** (10.7 mg, 22 μmol, 14%), **11** (2.9 mg, 6 μmol, 4%) and **6** (23 mg, 47 μmol, 29%).

Method C: potassium fluoride. To a solution of product **5** (500 mg, 1.5 mmol) and 3-methyl-1-nitrobutane[31] in *iso*-PrOH (30 ml) was added KF (174 mg, 3 mmol). The mixture was stirred for 24 h and poured in water. The aqueous phase was extracted with ether (3×20 ml), dried with Na_2SO_4, evaporated under vacuum and the residue was purified by flash chromatography (see method A) to give **9** (72 mg, 148 μmol, 10%), **10** (72 mg, 148 μmol, 10%), **11** (91 mg, 187 μmol, 12%) and **6** (144 mg, 296 μmol, 20%).

Method D: t-BuOK. To a solution of **5** (37 mg, 0.1 mmol) and 3-methyl-1-nitrobutane[31] (21 mg, 0.18 mmol) in *t*-BuOH/THF (1:1) (1 ml) was added *t*-BuOK (1 M/*t*-BuOH) (0.01 ml, 0.01 mmol). The reaction mixture was stirred at −25 °C during 2 days. Water was added and aqueous phase was extracted with ether (3×20 ml). Combined organic phases were dried with Na_2SO_4, filtered and evaporated under vacuum. Purification by flash chromatography (see method A) gave the four isomers **9** (6.1 mg, 13 μmol, 13%), **10** (8.5 mg, 18 μmol, 18%), **11** (4.4 mg, 9 μmol, 9%) and **6** (15 mg, 30 μmol, 30%).

The procedure with *t*-BuOLi and **5** (37 mg, 0.1 mmol) was the same and gave the four isomers: **9** (5.4 mg, 11 μmol, 11%), **10** (7.5 mg, 16 μmol, 16%), **11** (6.5 mg, 13 μmol, 13%)and **6** (14.5 mg, 30 μmol, 30%).

Method E: Amberlyst A-21. To a solution of **5** (37 mg, 0.1 mmol) and 3-methyl-1-nitrobutane (21 mg, 0.18 mmol) in THF was added Amberlyst A-21 (excess). The suspension was stirred 48 h, filtered and the resin was washed with THF. Evaporation under vacuum and purification by flash chromatography (see method A) gave the four isomers: **9** (4.9 mg, 10 μmol, 10%), **10** (8.4 mg, 17 μmol, 17%), **11** (5.8 mg, 12 μmol, 12%) and **6** (9.9 mg, 20 μmol, 20%).

3.1.5. ((*S*)-1-{(*S*)-(*tert*-Butyldimethylsilanyloxy)-[(*R*)-2-(*tert*-butyldiphenylsilanyloxymethyl)-tetrahydrofuran-(*R*)-3-yl]-methyl}-3-methylbutyl)-carbamic acid *tert*-butyl ester (7). To a solution of **6** (229 mg, 0.47 mmol) in CH_2Cl_2 (4.7 ml) at 0 °C was added 2,6-lutidine (164 μl, 1.41 mmol) and TBSOTf (216 μl, 0.94 mmol) and reaction was stirred for 24 h at room temperature. After addition of ether, the organic phase was washed with 1 N HCl, saturated aqueous $NaHCO_3$, and brine. Drying with Na_2SO_4, evaporation under vacuum and purification by flash chromatography (5% AcOEt/hexanes) gave the TBS ether derivative (259 mg, 433 μmol, 90%); $[\alpha]_D^{20}$ −24.5° (*c* 1.32, $CHCl_3$); IR (film) (cm^{-1}) 1556 (NO_2); NMR ^1H ($CDCl_3$, 400 MHz) δ (ppm) 7.72–7.68 (m, 4H), 7.48–7.41 (m, 6H), 4.61–4.55 (ddd, J=11.5, 8.6, 2.7 Hz, 1H), 4.31–4.29 (d, J=8.3 Hz, 1H), 3.95–3.82 (m, 3H), 3.79–3.75 (dd, J=3.9, 10.6 Hz, 1H), 3.74–3.70 (dd, J=5.2, 10.6 Hz, 1H), 2.49–2.43 (q, J=8.4 Hz, 1H), 2.22–2.13 (m, 1H), 2.01–1.94 (m, 1H), 1.84–1.76 (m, 1H), 1.54–1.39 (m, 2H), 1.10 (s, 9H), 0.99–0.97 (d, J=6.2 Hz, 3H), 0.95–0.94 (d, J=6.3 Hz, 3H), 0.89 (s, 9H), 0.07 (s, 3H), 0.02 (s, 3H); NMR ^{13}C ($CDCl_3$, 100 MHz) δ (ppm) 136.1, 136.0, 133.5, 130.3, 130.2, 128.2, 128.2, 92.3, 80.4, 73.6, 68.8, 65.7, 43.8, 39.6, 27.3, 26.4, 25.6, 25.6, 23.9, 21.3, 19.7, 18.8, −4.0, −4.3; MS 522.3 ($M-C_6H_5$); HRMS: calcd 599.3462; found, 599.3459.

To a solution of the above compound (200 mg, 0.33 mmol) in MeOH (3.3 ml) was added Raney-Ni (catalytic amount) and H_2PtCl_6 (ca 5 mg) and the mixture was stirred under H_2 (5 atm) for 16 h. After filtration through Celite and evaporation under vacuum, the residue was dissolved in MeOH and the reduction was continued for 3 days. After filtration through Celite and evaporation under vacuum, the residue was dissolved with THF/Et_3N (9:1) (3.3 ml) and Boc_2O (87 mg, 0.4 mmol) was added. After 5 h of stirring, the solvents were removed under vacuum and the residue was purified by chromatography (5% AcOEt/hexanes) to give **7** (199 mg, 297 μmol, 90%); IR (film) (cm^{-1}) 1715 (C=O); NMR ^1H ($CDCl_3$, 400 MHz) δ (ppm) 7.71–7.70 (m, 4H), 7.43–7.38 (m, 6H), 4.54–4.52 (d, J=9.3 Hz, 1H), 3.86–3.61 (m, 7H), 2.27–2.25 (m, 1H), 2.15–2.07 (m, 1H), 1.86 (m, 1H), 1.70–1.58 (m, 1H), 1.42 (s, 9H), 1.33–1.23 (m, 2H), 1.08 (s, 9H), 0.93 (m, 15H), 0.14–0.09 (2s, 6H); NMR ^{13}C ($CDCl_3$, 100 MHz) δ (ppm) 155.9, 136.1, 133.9, 133.8, 130.0, 128.1, 82.1, 79.4, 73.7, 68.7, 66.5, 53.6, 45.7, 42.3, 28.9, 27.8, 27.5, 27.3, 26.6, 25.2, 23.9, 22.5, 19.6, 18.8, −3.3, −3.6; MS 670.5 (M+1); HRMS: calcd 669.4245; found, 669.4240.

3.1.6. (*R*)-3-[(*S*)-2-*tert*-Butoxycarbonylamino-(*S*)-1-(*tert*-butyldimethylsilanyloxy)-4-methylpentyl]-tetrahydrofuran-(*R*)-2-carboxylic acid methyl ester (8). To a solution of **7** (104 mg, 155 μmol) in THF (1.5 ml) was added a TBAF/AcOH solution (1:1) (0.5 M) (340 μl) and the mixture was stirred 16 h, then poured in water (5 ml).

After extraction of the aqueous phase with ether (3×15 ml), the organic phase was washed with saturated aqueous $NaHCO_3$, and brine. Drying with Na_2SO_4, evaporation under vacuum and purification by flash chromatography (20% AcOEt/hexanes) gave the free alcohol (27 mg, 62 μmol, 40%); $[\alpha]_D^{20}$ −48.3° (*c* 1, $CHCl_3$); IR (film) (cm^{-1}) 3336 (OH), 1702 (C═O); NMR ^1H ($CDCl_3$, 400 MHz) δ (ppm) 4.57–4.55 (d, *J*=9.2 Hz, 1H), 3.83–3.80 (m, 2H), 3.74–3.68 (m, 3H), 3.62–3.49 (m, 1H), 2.37–2.34 (t, *J*=6.0 Hz, 1H), 2.18–2.12 (m, 1H), 2.08–1.98 (m, 1H), 1.93–1.85 (m, 1H), 1.66–1.56 (m, 1H), 1.44 (s, 9H), 1.31–1.25 (m, 2H), 0.93–0.92 (m, 15H), 0.13–0.10 (2s, 6H); NMR ^{13}C ($CDCl_3$, 100 MHz) δ (ppm) 156.1, 82.4, 79.7, 73.9, 68.2, 64.2, 52.6, 44.1, 32.3, 28.8, 28.7, 26.5, 25.2, 23.8, 22.4, 18.8, −3.2, −3.6; MS 432.3 (M+1); HRMS: calcd 431.3067; found, 431.3061.

To a solution of the above compound (20 mg, 46 mmol) in DMF (0.46 ml) was added PDC (87 mg, 230 mmol) and the mixture was stirred 2 days, then quenched with saturated aqueous $NaHCO_3$. After extraction with ether (3×15 ml), the aqueous phase was acidified with 1 N HCl to pH 4. A second extraction with ether (2×15 ml) was followed by acidification with 1 N HCl to pH 1. Drying of the combined organic phases and evaporation under vacuum gave the acid that was dissolved in MeOH and cooled to 0 °C. A solution of CH_2N_2 in ether was added dropwise until the yellow color persisted for several minutes. A few drops of AcOH were added to neutralize excess CH_2N_2. Evaporation under vacuum, and purification by flash chromatography (10% AcOEt/hexanes) gave **8** (12 mg, 26 μmol, 57%); $[\alpha]_D^{20}$ −46.8° (*c* 0.6, $CHCl_3$); IR (film) (cm^{-1}) 1711 (C═O); NMR ^1H ($CDCl_3$, 400 MHz) δ (ppm) 4.66–4.64 (d, *J*=9.0 Hz, 1H), 4.24–4.23 (d, *J*=7.3 Hz, 1H), 3.99–3.90 (m, 3H), 3.78 (s, 3H), 3.74 (m, 1H), 2.52–2.45 (m, 1H), 2.09–2.02 (m, 1H), 2.00–1.90 (m, 1H), 1.67–1.62 (m, 1H), 1.45 (s, 9H), 1.42–1.36 (m, 1H), 1.30–1.23 (m, 1H), 0.96–0.94 (m, 15H), 0.19–0.14 (2s, 6H); NMR ^{13}C ($CDCl_3$, 100 MHz) δ (ppm) 174.3, 155.8, 79.5, 73.5, 69.7, 53.3, 52.5, 48.1, 41.3, 28.8, 28.2, 26.5, 25.3, 23.8, 22.4, 18.7, −3.3, −3.9; MS 460.4 (M+1); HRMS: calcd 459.3016; found, 459.3011.

4. Supporting Information

X-ray structure data for compounds **6**, **9**, **10**, **11**. See also Cambridge Data Base.

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