EurJOC
European Journal of Organic Chemistry

A Journal of
ChemPubSoc Europe

Accepted Article

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To be cited as: *Eur. J. Org. Chem.* 10.1002/ejoc.201701289

Link to VoR: http://dx.doi.org/10.1002/ejoc.201701289

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10.1002/ejoc.201701289

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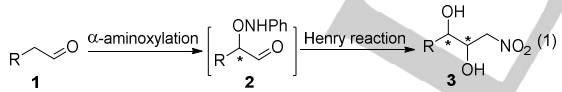
Organocatalytic Asymmetric Tandem α-Aminooxylation-Henry Reactions for the Synthesis of 1,2-Diols: Total Synthesis of (-)-L-*threo*-Sphinganine

Yuvraj Garg,[a] Ramandeep Kaur[a] and Satyendra Kumar Pandey*[a]

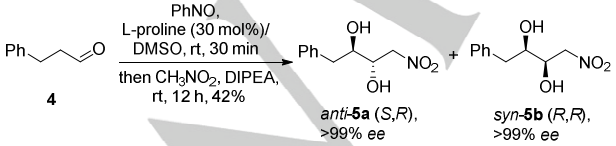
Abstract: A novel and rapid asymmetric syntheses of 1,2-diol derivatives *anti*- and *syn*-β,γ-dihydroxynitroalkanes *via* organocatalyzed tandem α-aminooxylation-Henry reactions are described. The targeted diol derivatives are synthesized in good yields, with excellent enantio- and low to moderate diasteroselectivities under mild conditions. Synthesis of an antineoplastic and antipsoriatic drug (-)-L-*threo*-sphinganine demonstrate the synthetic utility of the fragments generated in the title reaction.

Enantiopure 1,2-diols are versatile chiral building blocks and have been used widely as starting materials for the asymmetric synthesis of drugs and bioactive natural products.[1] Various methods for the synthesis of 1,2-diols have been documented in the literature.[2,3] The Sharpless asymmetric dihydroxylation (AD) of *trans*-olefins[3] is one of the most efficient reactions leading to *syn*-1,2-diols in high enantiomeric excesses (*ee*'s) while *cis*-olefins give rise to *anti*-1,2-diols showing low enantioselectivity.[3b] Recent developments in asymmetric catalysis have included organocatalysis involving α-aminooxylation directed tandem reactions which demonstrate a rapid and atom-economical one pot catalytic process that provides enantiopure compounds.[4] We envisioned that reactive α-aminooxy aldehyde intermediate **2** generated from the organocatalyzed α-aminooxylation[2l-n] of aldehydes **1** on *in situ* trapping with nitromethane under a Henry reaction conditions[5] followed by cleavage of phenylamine moiety would provide β,γ-dihydroxynitroalkane **3** (eq 1).

Based on this, herein we describe a highly enantioselective one-pot tandem approach to a non-terminal 1,2-diol unit β,γ-dihydroxynitroalkanes involving the organocatalyzed α-aminooxylation of aldehydes followed by an *in situ* Henry reaction. Our preliminary experiments were initiated by using 3-



phenylpropionaldehyde **4** as the model substrate, nitrosobenzene, DMSO as the solvent and L-proline as the catalyst (Scheme 1).



Scheme 1. Strategy for *in situ* trapping of the reactive α-aminoxylated aldehyde intermediates.

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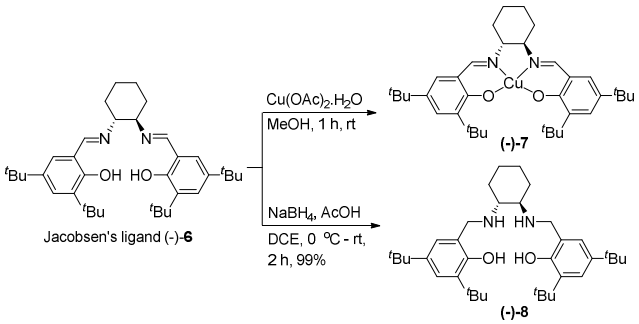
Nitromethane and base DIPEA were used in the second step and were added to α-aminooxylation reaction mixture until all the nitrosobenzene was consumed. Pleasingly, the tandem reaction proceeded smoothly with product *anti*-**5a** and *syn*-**5b** in 42% yield along with expected *O*-NHPh protected derivative of **5** in low yield (12%). It is also known that *in situ* partial N-O bond cleavage may occur during α-aminooxylation reaction.[2i] It is also worthy to mention that removal of *N*-phenylamino group could be achieved by either catalytic hydrogenation[2n] or by Cu(II) catalyzed reactions.[6] The separation of *anti*-**5a** and *syn*-**5b** on silica gel column chromatography indicated no diastereoselectivity in the second step (*anti*-**5a**/*syn*-**5b** 1:1), but excellent enantioselectivities were found (>99% *ee* for each of *anti*-**5a** and *syn*-**5b**) in one pot tandem α-aminooxylation-Henry reactions.

Guided by our favorable results, we then focused on using a chiral catalyst in the Henry reaction to improve the diastereoselectivity and chemical yield. After the first report of Shibasaki and co-workers,[5y] many efforts have been made continuously in the literature for asymmetric induction into the Henry reaction, using prochiral aldehydes and nitromethane in the presence of chiral metal complexes and organocatalysts.[5] Among them, Henry reaction catalyzed by the stable Cu(II)-salen complex has received more attention during the recent years.[5i-s] Towards this end, a stable copper (II)-salen complex (-)-**7** was prepared by the treatment of commercially available (*R*,*R*)-Jacobsen's ligand[7] (-)-**6** with copper (II) acetate in methanol (Scheme 2) which was then used in tandem α-aminooxylation-Henry reactions. Initial result was not encouraging, as the tandem reaction proceeded with no improvement in *anti*-**5a**/*syn*-**5b** diastereomeric ratio even though with no loss in enantiomeric excess (*ee*'s).

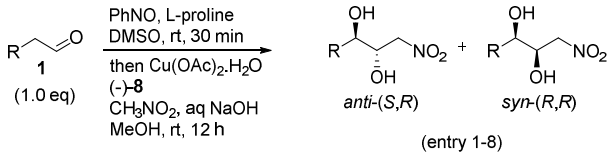
We next envisioned that, due to the strong basicity and coordination capability of the secondary diamine ligands could affect the catalytic activity in the Cu catalyzed Henry reaction.[5i-l,n,p,r] Therefore, we have performed the reduction of ligand (-)-**6** with $NaBH_4$/acetic acid in DCE to diamine ligand (-)-**8** in excellent yield of 99% which was used further for controlling the stereoselectivity (Scheme 2).



Scheme 2. Synthesis of (-)-**7**/copper (II) complex and tetrahydrosalen ligand (-)-**8** from (-)-**6**.

Serendipitously, ligand (-)-**8** on complexation with $Cu(OAc)_2.H_2O$ led to more promising outcome in the Henry reaction step to furnish relatively good yield of *anti*-**5a**/*syn*-**5b** in 52% without affecting the enantioselectivity. To further improve the diastereoselectivity and chemical yield, a series of other Cu (I) catalysts, such as CuI, CuBr, CuCl, CuCN, CuOAc and Cu (II) catalysts, such as $CuCl_2.2H_2O$, $Cu(OTf)_2$, $CuSO_4.5H_2O$ were surveyed in the presence of ligand (-)-**8**. Out of copper (I) and (II) catalysts, $Cu(OAc)_2.H_2O$ turned out to be the best choice for subsequent reactions which provided the highest *anti*/*syn* ratio.

Table 1. Asymmetric synthesis of *β,γ*-dihydroxynitroalkane derivatives under optimized conditions.



entry	product	R	Yield[a] (%)	dr[b] (*anti*/*syn*)	*ee*[c] (*anti*/*syn*, %)
1	**5**	Bn	67	1.37:1	99/92
2	**9**	*i*-Pr	64	1.35:1	>99/98
3	**10**	Me	67	1.75:1	98/94
4	**11**	C_4H_9	64	1.23:1	92/96
5	**12**	C_5H_{11}	62	6.34:1	98/82
6	**13**	C_7H_{15}	67	1.10:1	90/>99
7	**14**	$C_{10}H_{21}$	70	3.30:1	>99/98
8	**15**	$C_{15}H_{31}$	68	1.20:1	80/>99
9	**5**[d]	Bn	62	1.10:1	>99/96
10	**14**[d]	$C_{10}H_{21}$	65	1.10:1	70/96
11	**15**[d]	$C_{15}H_{31}$	67	1.64:1	86/97

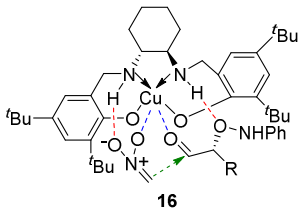
[a]All were for isolated *anti*+*syn* products. [b]The *anti*/*syn* diastereomeric ratio was determined by chiral HPLC. All diastereomers were separable from the silica gel column chromatography. [c]The *ee*'s were determined by HPLC on Chiralpak IA, AD-H and Chiralcel OJ-H columns (see Supporting Information). [d]The *α*-aminooxylation reaction was performed *via* using D-proline as catalyst which furnished the *anti*-(*R*,*S*) and *syn*-(*S*,*S*) diastereomers (entry 9-11). The *α*-aminooxylated aldehydes are known to present in the form of oligomer in solution.[2m]

After establishing the choice of catalyst, we moved further to screen the reaction solvents for tandem *α*-aminooxylation-Henry reactions. Previously, Guofu Zhong[2n] reported that DMSO acts as best solvent for *α*-aminooxylation in terms of yield and enantioselectivity. However, among the solvents (DMSO, CH_3CN, MeOH, EtOH, DCM, IPA, DMF, Toluene, THF, 1,4-dioxane) screened for Henry reaction on *α*-aminooxylated aldehyde intermediates, polar protic solvent methanol was found to be best with respect to optical purity and chemical yield.

It is well known that a base could be employed in Henry reaction to generate the nitronate ion from nitromethane and to increase the reactivity of the catalyst.[5s] Among the screened bases (aq NaOH, aq KOH, K_2CO_3, K-O^{t}Bu, DIPEA, DMAP, NEt_3, NMM and DBU) for Henry reaction of nitromethane with *α*-aminooxylated aldehyde intermediates in methanol, aq NaOH was found to show the best reactivity for the *anti*-**5a**/*syn*-**5b**.

With optimal reaction conditions in hand, we further explored the scope of this one-pot tandem approach to a variety of *α*-aminooxylated aromatic and aliphatic aldehyde intermediates (Table 1). The tandem reaction furnished the adducts in low to moderate diastereoselectivities of *anti*/*syn* ratio (from 1.10:1 to 6.34:1), excellent enantioselectivity (up to >99% *ee*'s) and good overall yields (up to 70%). The described tandem reaction does not require oxygen free or anhydrous conditions and was completed in 12 h at room temperature. The stereochemistry of this tandem transformation was assigned *via* ^{1}H-NMR determination of the *anti*- and *syn*-diastereomers which are in accordance with the previously established absolute configuration of the *α*-aminooxylated aldehyde.[2l-n]

As evident from Table 1 results that there is preference of (1*R*,2*R*)-ligand (-)-**8**/Cu(II) complex to give *anti*-*β,γ*-dihydroxynitroalkane derivatives during tandem *α*-aminooxylation-Henry reactions approach. This implies that nitronate ion attack at the *si* face of the *α*-aminooxylated aldehyde synthesized using the L-proline; to rationalize the outcome, a transition state **16** is proposed in Figure 1. In the proposed model, substrates are coordinated to (-)-**8**/Cu(II) complex under the bicyclic framework and C-C bond formation taking place from the less hindered side due to two simultaneously NH hydrogen bonding, one with *O*-NHPh of *α*-aminooxylated aldehyde and another with the nitronate ion. Since, in complex (-)-**7** this hydrogen bonding was absent leads to low or no diastereoselectivity.



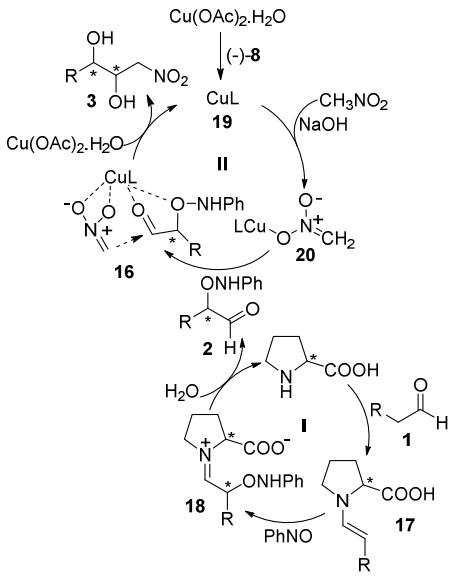
16

Figure 1. Plausible transition state for the tandem *α*-aminooxylation-Henry reactions.

As a probe to the mechanism, the *α*-aminooxylated aldehyde synthesized from D-proline was subjected to *in situ* treatment with nitromethane under the above optimized Henry reaction conditions which furnished the *anti*-selective diastereomer (*re* face attack) of *β,γ*-dihydroxynitroalkane in good yield and *anti*-**5c**/*syn*-**5d** 1.10:1 diastereomeric ratio (Table 1, **5**[d]). The results imply that the NH hydrogen bonding with *O*-NHPh of *α*-aminooxylated aldehyde furnished the more *anti*-selective diastereomeric ratio from both L- and D-proline.

Based on our study and literature reports, a catalytic cycle that would incorporate a transition state **16** is proposed in Scheme 3. In the first cycle, the aldehyde **1** on *α*-aminooxylation would provide the enantiopure *α*-aminooxylated aldehyde intermediate **2** *via* reactive intermediates **17** and **18** which then undergo stereocontrolled Henry reaction. In the second cycle, ligand exchange of tetrahydrosalen (-)-**8** for acetic acid would afford complex **19**, which on further progress *via* Cu (II) complex **20** and transition state **16** complete the cycle while generating the *β,γ*-dihydroxynitroalkane derivative **3**.

We next explored the synthetic application of the *β,γ*-dihydroxynitroalkane fragments produced in the tandem *α*-aminooxylation-Henry reactions. The 1,2-diols and vicinal amino-alcohols motifs are found in various drugs and bioactive natural products such as antineoplastic and antipsoriatic drug



Scheme 3. Proposed catalytic cycle for the synthesis of *β,γ*-dihydroxynitroalkane derivatives.

L-*threo*-sphinganine (safingol) **21**,[8a] potent inhibitor of the serine/threonine kinases protein kinase A, protein kinase C drug (*R,R*)-balanol **22**,[8b] antidepressant drug (*S,S*)-reboxetine **23**,[8c] hydroxylated piperdines with potent antimalarial drug febrifugine **24**,[8d] and antibiotic (-)-galantinic acid **25**[8e] (Figure 2).

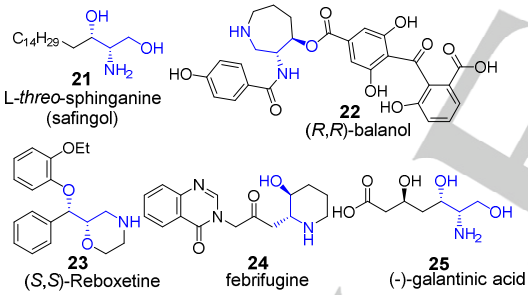
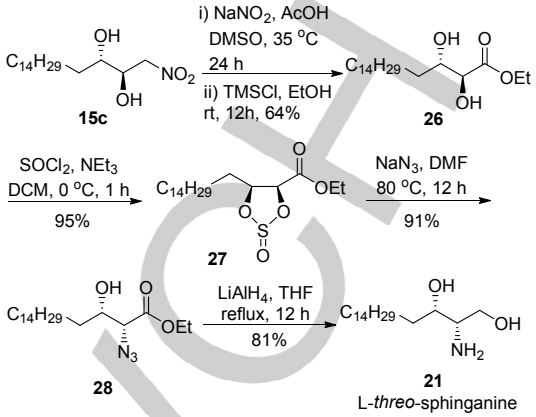


Figure 2. Some selected biologically active compounds.

In continuation of our ongoing research programme towards the asymmetric syntheses of bioactive compounds,[9] we demonstrated the synthetic application of the developed tandem *α*-aminooxylation-Henry reactions towards the total synthesis of L-*threo*-sphinganine **21**.[10]

With enantiomerically pure *anti*-**15c** (Table 1, **15**[d]) diastereomer in hand, we then subjected it to $NaNO_2$/acetic acid mediated oxidation in DMSO to furnish acid[1b,e] which on spontaneous treatment with TMSCl/EtOH[11] afforded the *α,β*-dihydroxy ester **26** in 64% yield (Scheme 4). The diol **26** on treatment with thionyl chloride under basic conditions at 0 °C furnished the cyclic sulfite **27** in 95% yield. The regioselective nucleophilic opening of cyclic sulfite **27** at the *α*-carbon position with NaN_3/DMF at 80 °C afforded the *α*-azido-*β*-hydroxy ester **28** in 91% yield. Finally, concomitant reduction of ester and azide groups of derivative **28** with $LiAlH_4$ in THF at 70 °C afforded the target L-*threo*-sphinganine **21** in 81% yield {$[\alpha]_D^{25}$ -7.5 (*c* 0.09, C_2H_5OH) Lit.[10a] -7.6 (*c* 0.09, C_2H_5OH)}.



Scheme 4. Asymmetric synthesis of L-*threo*-sphinganine.

In conclusion, we have developed a novel organocatalyzed tandem *α*-aminooxylation-Henry reactions approach for the asymmetric synthesis of *anti*- and *syn*-*β,γ*-dihydroxynitroalkane derivatives in good yield (up to 70%) with excellent enantio- (*ee*'s for *anti*- and *syn* up to >99%) and diastereselectivities (dr *anti*/*syn*, up to 6.34:1). The (*S*)- and (*R*)- configuration of *α*-aminooxylated aldehyde could be manipulated by simply changing the D-proline and L-proline, respectively, during organocatalytic step and thus, in principle, all the four isomers of *β,γ*-dihydroxynitroalkane derivatives could be accessed from this developed tandem approach. The rapid and protecting group free synthesis of an antineoplastic and antipsoriatic drug L-*threo*-sphinganine demonstrates the synthetic utility of the chiral building blocks furnished by the title reaction. This tandem strategy, which is amenable to both *anti*- and *syn*-1,2-diols, has significant potential for its further extension to the asymmetric synthesis of a variety of natural- and natural-like bioactive compounds.

Experimental Section

General Experimental Details: The chemicals and solvents were purchased from Merck and Sigma Aldrich chemical company. Progress of the reactions was monitored by thin layer chromatography using precoated aluminium plates of Merck kieselgel 60 F254. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ (unless otherwise mentioned) on JEOL ECS operating at 400 and 100 MHz, respectively. Chemical shifts are reported in *δ* (ppm), referenced to TMS. IR spectra were recorded on Agilent resolution Pro 600 FT-IR spectrometer, fitted with a beam-condensing ATR accessory and peaks are reported in cm^{-1}. HRMS were recorded using Electron Spray Ionization. UV-vis spectrum was recorded on UV 2600 Shimadzu spectrophotometer. Optical rotations were measured on Automatic polarimeter AA-65 and concentrations of g/100 mL. Column chromatography was performed on silica gel (60-120 and 100-200 mesh) using a mixture of hexane/ethyl acetate and dichloromethane/MeOH. All reactions were carried out under argon or nitrogen atmosphere, in oven-dried glassware using standard glass syringes, cannulas and septa (unless otherwise mentioned). Solvents and reagents were purified and dried by standard methods prior to use (unless otherwise mentioned). The diastereomer ratio (dr) and

enantiomeric purity (*ee*) were determined by Waters HPLC analysis using Chiralpak IA, AD-H and Chiralcel OJ-H chiral columns.

6,6'-((((1*R*,2*R*)-Cyclohexane-1,2-diyl)bis(azanediyl))bis(methylene)) bis(2,4-di-*tert*-butyl phenol) (8): To a dichloroethane (20 mL) solution of (*R*,*R*)-Jacobsen's ligand (-)-**6** (2.0 g, 3.65 mmol) was added $NaBH_4$ (278 mg, 7.30 mmol) followed by acetic acid (2 mL) at 0 °C. The reaction mixture was stirred at room temperature for 2 h and then quenched with saturated aqueous $NaHCO_3$ solution. The aqueous phase was extracted with EtOAc (3 x 20 mL), dried over anhydrous Na_2SO_4, concentrated *in vacuo*, and purified by silica gel column chromatography (EtOAc/hexanes 1:1 v/v) as eluent to afford the ligand (-)-**8** (1.99 g, 99%). $\{[\alpha]_D^{25}$ -14.0 (*c* 0.5, CH_3OH); IR (CH_2Cl_2) *v*: 3491, 3272, 2961, 2908, 2878, 1472, 1435, 1421, 1391, 1247, 991, 733 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) *δ*: 7.21 (d, *J* = 2.76 Hz, 2H), 6.86 (d, *J* = 2.28 Hz, 2H), 4.04 (d, *J* = 13.2 Hz, 2H), 3.90 (d, *J* = 13.2 Hz, 2H), 2.47-2.46 (m, 2H), 2.19-2.16 (m, 2H), 1.71-1.70 (m, 2H), 1.45-1.40 (m, 20H), 1.28-1.21 (m, 24H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 154.3, 140.5, 135.9, 123.1, 122.9, 122.3, 59.8, 50.8, 34.8, 34.1, 31.6, 30.7, 29.5, 24.1. HRMS $(ESI)^+$ m/z calcd for $C_{36}H_{58}N_2O_2Na^+$ ($[M+Na]^+$) 573.4390; found 573.4391.

General Procedure for tandem *α*-aminooxylation-Henry reaction: To a DMSO (1.5 mL) solution of aldehyde (1.0 mmol) and nitrosobenzene (1.0 mmol), L- or D-proline (30 mol%) was added and stirred for about 20-30 min at room temperature. The completion of the reaction was monitored by its colour change from green to orange or by TLC until all the nitrosobenzene was consumed and used as such for the next step without further purification. The ligand (-)-**8** (0.055 mmol, 5.5 mol%) and $Cu(OAc)_2.H_2O$ (0.05 mmol, 5 mol%) were added to methanol (1.5 mL) and reaction mixture was stirred for 1 h at room temperature. To the resulting dark blue solution of the catalyst, solvent (1.5 mL), nitromethane (10.0 mmol), base (1.5 mmol), and above synthesized *α*-aminooxylatedaldehyde (1.0 mmol) were added. The reaction mixture was stirred for 30 min then $Cu(OAc)_2.H_2O$ (1.5 mmol) was added and further stirred for 12 h at room temperature. After completion of the reaction (monitored by TLC), the reaction mixture was evaporated, diluted with water, extracted with EtOAc, dried over Na_2SO_4, concentrated and purified by silica gel column chromatography.

(-)-8/Cu(II) complex (19): To a MeOH (1.5 mL) solution of ligand (-)-**8** (30 mg, 0.055 mmol) was added $Cu(OAc)_2.H_2O$ (10 mg, 0.05 mmol) and stirred for 1 h at room temperature under air atmosphere. After completion of the reaction (as monitored by TLC), the reaction mixture was evaporated, diluted with water, extracted with EtOAc, dried over Na_2SO_4, concentrated and purified by silica gel column chromatography using (EtOAc/hexane 1:4 v/v) as eluent to furnish the complex **19** (30 mg, 95% yield) as green solid. $\{[\alpha]_D^{25}$ -558.4 (*c* 0.07, $CHCl_3$) [Lit.[5j] -558.8 (*c* 0.068, $CHCl_3$)]; IR (CH_2Cl_2) *v*: 3435, 3262, 3212, 2950, 2864, 2590, 2283, 1689, 1600, 1467, 1439, 1412, 1361, 1236, 1165, 1012, 926, 877, 827, 780, 738, 460 cm^{-1}; UV-vis (CH_2Cl_2) λ_{max}: 612, 410, 292, 248 nm [Lit.[5j] λ_{max}: 623, 423, 290, 246 nm]; HRMS $(ESI)^+$ m/z calcd for $C_{36}H_{57}N_2O_2Cu^+$ ($[M+H]^+$) 612.3711; found 612.3724.

(*anti*/*syn*)-1-Nitro-4-phenylbutane-2,3-diol (5a and 5b): Following the general procedure for tandem *α*-aminooxylated-Henry reaction, the residue obtained was purified by silica gel column chromatography using (EtOAc/hexane 1:5 v/v) as eluent to furnish the *anti*-**5a** and *syn*-**5b** diastereomers as white solid in 67% yield (142 mg, 0.67 mmol), (99% *ee* for *anti*-**5a**, 92% *ee* for *syn*-**5b**) and as 1.37:1 *anti*:*syn* mixture of diastereomers. IR (CH_2Cl_2) *v*: 3512, 3127, 2936, 1620, 1553, 1423, 1375, 791 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) *δ*: 7.35-7.21 (m, 5H), 4.72-4.45 (m, 2H), 4.28-4.21 (m, 1H), 3.90-3.79 (m, 1H), 3.05-2.67 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 136.7, 136.6, 129.3, 129.2, 128.9, 127.0, 127.0, 78.6, 77.6, 73.2, 72.5, 71.2, 69.8, 39.9, 39.4. The diastereomer ratio (dr) and enantiomeric purity (*ee*) were determined by HPLC analysis using a Chiralcel AD-H chiral column (4.6 x 250 mm) using mobile phase of (9:1 hexane/*i*-PrOH, flow rate of 1 mL/min at 25 °C, UV detection at 215 nm): *anti* diastereomer (*S*,*R*)-enantiomer: t_r = 11.202 min, (*R*,*S*)-enantiomer: t_r = 12.012 min; *syn* diastereomer (*R*,*R*)-enantiomer: t_r = 8.866 min, (*S*,*S*)-enantiomer: t_r = 10.652 min.

(2*R*,3*R*)-1-Nitro-4-phenylbutane-2,3-diol (5b): The above *anti*-/*syn*-diastereomers **5** (142 mg) were separated and purified by silica gel column chromatography using (EtOAc/hexane 1:9 v/v) as eluent to furnish the *syn*-**5b** diastereomer as white solid in 28% yield (57 mg, 0.28 mmol) with 97% *ee*. $[\alpha]_D^{25}$ -25.4 (*c* 0.2, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) *δ*: 7.37-7.22 (m, 5H), 4.75-4.52 (m, 2H), 4.27-4.23 (m, 1H), 3.91-3.86 (m, 1H), 3.07-3.03 (m, 1H), 2.95-2.88 (m, 1H), 2.69-2.75 (m, 1H), 1.97 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 136.5, 129.3, 128.9, 127.1, 77.6, 73.1, 71.2, 39.5. HRMS $(ESI)^+$ m/z calcd for $C_{10}H_{13}NO_4Na^+$ ($[M+Na]^+$) 234.0737; found 234.0728. The enantiomeric purity (*ee*) was determined by HPLC analysis using a Chiralcel AD-H chiral column (4.6 x 250 mm) using mobile phase of (9:1 hexane/*i*-PrOH, flow rate of 1 mL/min at 25 °C, UV detection at 215 nm): (*R*,*R*)-enantiomer: t_r = 8.697 min, (*S*,*S*)-enantiomer: t_r = 10.580 min.

(2*S*,3*R*)-1-Nitro-4-phenylbutane-2,3-diol (5a): After separation of the *syn*-**5b** diastereomer, the *anti*-**5a** diastereomer was quickly eluted (EtOAc/hexane 1:4 v/v) as white solid in 39% yield (84 mg, 0.39 mmol) with >99% *ee*. $[\alpha]_D^{25}$ -8.2 (*c* 0.6, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) *δ*: 7.36-7.21 (m, 5H), 4.65-4.46 (m, 2H), 4.29-4.25 (m, 1H), 3.83-3.82 (m, 1H), 2.95-2.87 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 136.7, 129.3, 129.2, 128.9, 127.0, 78.6, 72.5, 69.7, 39.9. HRMS $(ESI)^+$ m/z calcd for $C_{10}H_{13}NO_4Na^+$ ($[M+Na]^+$) 234.0737; found 234.0735. The enantiomeric purity (*ee*) was determined by HPLC analysis using a Chiralcel AD-H chiral column (4.6 x 250 mm) using mobile phase of (9:1 hexane/*i*-PrOH, flow rate of 1 mL/min at 25 °C, UV detection at 215 nm): (*S*,*R*)-enantiomer: t_r = 11.108 min, (*R*,*S*)-enantiomer: t_r = 11.854 min.

(*anti*/*syn*)-1-Nitro-4-phenylbutane-2,3-diol (5c and 5d): Following the general procedure for tandem *α*-aminooxylated-Henry reaction, the residue was purified by silica gel column chromatography using (EtOAc/hexane 1:4 v/v) as eluent to afford the *anti*-**5c** and *syn*-**5d** diastereomers as white solid in 62% yield (131 mg, 0.62 mmol), (>99% *ee* for *anti*-**5c**, 96% *ee* for *syn*-**5d**) and as 1.10:1 *anti*:*syn* mixture of diastereomers. ^1H NMR (400 MHz, $CDCl_3$) *δ*: 7.35-7.15 (m, 5H), 4.69-4.42 (m, 2H), 4.26-4.21 (m, 1H), 3.89-3.77 (m, 1H), 3.01-2.65 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 136.8, 129.3, 129.3, 129.2, 128.8, 128.5, 126.9, 126.9, 78.6, 77.6, 73.3, 72.6, 71.3, 69.8, 39.8, 39.3. The diastereomer ratio (dr) and enantiomeric purity (*ee*) were determined by HPLC analysis using a Chiralcel AD-H chiral column (4.6 x 250 mm) using mobile phase of (9:1 hexane/*i*-PrOH, flow rate of 1 mL/min at 25 °C, UV detection at 215 nm): *anti* diastereomer (*S*,*R*)-enantiomer: t_r = 11.073 min, (*R*,*S*)-enantiomer: t_r = 11.738 min; *syn* diastereomer (*R*,*R*)-enantiomer: t_r = 8.353 min, (*S*,*S*)-enantiomer: t_r = 10.341 min.

(*anti*/*syn*)-4-Methyl-1-nitropentane-2,3-diol (9): Following the general procedure for tandem *α*-aminooxylated-Henry reaction, the residue was purified by silica gel column chromatography using (EtOAc/hexane 1:6 v/v) as eluent to afford the *anti*-**9a** and *syn*-**9b** diastereomers as white solid in 64% yield (104 mg, 0.64 mmol), (>99% *ee* for *anti*, 98% *ee* for *syn*) and as 1.35:1 *anti*:*syn* mixture of diastereomers. IR (CH_2Cl_2) *v*: 3574, 3512, 2975, 2904, 2714, 1545, 1471, 1413, 1373, 1289, 1182, 1085, 1054, 931, 770 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) *δ*: 4.66-4.42 (m, 3H), 3.47-3.15 (m, 2H), 2.36 (br s, 1H), 1.91-1.76 (m, 1H), 1.03-0.97 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 79.2, 77.5, 77.5, 76.9, 69.6, 68.7, 30.7, 29.6, 18.9, 18.7, 18.2, 17.4. HRMS $(ESI)^-$ m/z calcd for $C_6H_{12}NO_4^-$ ($[M-H]^+$) 162.0772; found 162.0774. The diastereomer ratio (dr) and enantiomeric purity (*ee*) were determined by HPLC analysis using a

Chiracel OJ-H (4.6 x 250 mm) using mobile phase of (03:97 *i*-propanol/*n*-hexane, flow rate of 1.5 mL/min at 25 °C, UV detection at 220 nm): *anti* diastereomer (*R*,*S*)-enantiomer: t_r = 30.61 min, (*S*,*R*)-enantiomer: t_r = 28.97 min; *syn* diastereomer (*R*,*R*)-enantiomer: t_r = 21.40 min, (*S*,*S*)-enantiomer: t_r = 25.49 min.

(*anti*/*syn*)-1-Nitrobutane-2,3-diol (10): Following the general procedure for tandem *α*-aminooxylated-Henry reaction, the residue was purified by silica gel column chromatography using (EtOAc/hexane 1:3 v/v) as eluent to furnish the *anti*-**10a** and *syn*-**10b** diastereomers as white solid in 67% yield (90 mg, 0.67 mmol), (98% *ee* for *anti*, 94% *ee* for *syn*) and as 1.75:1 *anti*:*syn* mixture of diastereomers. IR (CH_2Cl_2) *v*: 3589, 3532, 2978, 2925, 1742, 1653, 1561, 1539, 1458, 1378, 1061, 771 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) *δ*: 4.64-4.49 (m, 2H), 4.24-4.16 (m, 1H), 3.97-3.76 (m, 1H), 2.98 (br s, 1H), 2.14 (br s, 1H), 1.32-1.26 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 78.3, 77.2, 72.3, 72.0, 68.6, 67.8, 19.5, 18.7. HRMS $(ESI)^-$ m/z calcd for $C_4H_8NO_4^-$ ($[M-H]^+$) 134.0459; found 134.0489. The diastereomer ratio (dr) and enantiomeric purity (*ee*) were determined by HPLC analysis using a Chirapak AD-H (4.6 x 250 mm) using mobile phase of (05:95 *i*-propanol:*n*-hexane, flow rate of 1 mL/min at 25 °C, UV detection at 220 nm): *anti* diastereomer (*S*,*R*)-enantiomer: t_r = 41.52 min, (*R*,*S*)-enantiomer: t_r = 44.67 min; *syn* diastereomer (*R*,*R*)-enantiomer: t_r = 46.79 min, (*S*,*S*)-enantiomer: t_r = 56.15 min.

(*anti*/*syn*)-1-Nitroheptane-2,3-diol (11): Following the general procedure for tandem *α*-aminooxylated-Henry reaction, the residue was purified by silica gel column chromatography using (EtOAc/hexane 1:4 v/v) as eluent to furnish the *anti*-**11a** and *syn*-**11b** diastereomers as white solid in 64% yield (113 mg, 0.64 mmol), (92% *ee* for *anti*, 96% *ee* for *syn*) and as 1.23:1 *anti*:*syn* mixture of diastereomers. IR (CH_2Cl_2) *v*: 3531, 3133, 2937, 1586, 1572, 1522, 1472, 1381, 1282, 1224, 1118, 1110, 770 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) *δ*: 4.62-4.48 (m, 2H), 4.27-4.22 (m, 1H), 3.77-3.54 (m, 1H), 2.65 (br s, 2H), 1.59-1.25 (m, 6H), 0.92 (t, *J* = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 78.7, 77.2, 72.9, 71.8, 71.7, 70.9, 33.0, 32.2, 27.7, 27.5, 22.4, 13.9. HRMS $(ESI)^-$ m/z calcd for $C_7H_{14}NO_4^-$ ($[M-H]^+$) 176.0928; found 176.0942. The diastereomer ratio (dr) and enantiomeric purity (*ee*) were determined by HPLC analysis using a Chirapak IA (4.6 x 150 mm) using mobile phase of (4:96:0.1 *i*-propanol:*n*-hexane:DEA, flow rate of 1 mL/min at 25 °C, UV detection at 230 nm): *anti* diastereomer (*S*,*R*)-enantiomer: t_r = 17.29 min, (*R*,*S*)-enantiomer: t_r = 15.38 min; *syn* diastereomer (*R*,*R*)-enantiomer: t_r = 18.53 min, (*S*,*S*)-enantiomer: t_r = 19.56 min.

(*anti*/*syn*)-1-Nitrooctane-2,3-diol (12): Following the general procedure for tandem *α*-aminooxylated-Henry reaction, the residue was purified by silica gel column chromatography using (EtOAc/hexane 1:4 v/v) as eluent to furnish the *anti*-**12a** and *syn*-**12b** diastereomers as white solid in 62% yield (118 mg, 0.62 mmol), (98% *ee* for *anti*, 82% *ee* for *syn*) and as 6.34:1 *anti*:*syn* mixture of diastereomers. IR (CH_2Cl_2) *v*: 3364, 3211, 1715, 1682, 1665, 1579, 1512, 1366, 1344, 1072 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) *δ*: 4.62-4.48 (m, 2H), 4.27-4.21 (m, 1H), 3.77-3.54 (m, 1H), 2.83 (br s, 2H), 1.57-1.32 (m, 8H), 0.90 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 78.7, 77.2, 72.8, 71.8, 71.7, 70.8, 33.3, 32.5, 31.5, 25.3, 25.1, 22.4, 13.9. HRMS $(ESI)^-$ m/z calcd for $C_8H_{16}NO_4^-$ ($[M-H]^+$) 190.1085; found 190.1095. The diastereomer ratio (dr) and enantiomeric purity (*ee*) were determined by HPLC analysis using a Chirapak AD-H (4.6 x 250 mm) using mobile phase of (5:95:0.1 *i*-propanol:*n*-hexane:DEA, flow rate of 1 mL/min at 25 °C, UV detection at 230 nm): *anti* diastereomer (*S*,*R*)-enantiomer: t_r = 18.11 min, (*R*,*S*)-enantiomer: t_r = 20.36 min; *syn* diastereomer (*R*,*R*)-enantiomer: t_r = 13.37 min, (*S*,*S*)-enantiomer: t_r = 14.41 min.

(*anti*/*syn*)-1-Nitrodecane-2,3-diol (13): Following the general procedure for tandem *α*-aminooxylated-Henry reaction, the residue was purified by silica gel column chromatography using (EtOAc/hexane 1:4 v/v) as eluent to furnish the *anti*-**13a** and *syn*-**13b** diastereomers as white solid in 67% yield (146 mg, 0.67 mmol), (90% *ee* for *anti*, >99% *ee* for *syn*) and as 1.10:1 *anti*:*syn* mixture of diastereomers. IR (CH_2Cl_2) *v*: 3459, 3122, 2962, 2877, 1732, 1652, 1591, 1561, 1466, 1371, 1265, 1092, 770 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) *δ*: 4.62-4.48 (m, 2H), 4.26-4.22 (m, 1H), 3.77-3.54 (m, 1H), 2.44 (br s, 2H), 1.58-1.21 (m, 12H), 0.88 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 78.7, 77.2, 72.8, 71.8, 71.7, 70.8, 33.4, 32.6, 31.7, 29.3, 29.1, 25.6, 25.4, 22.5, 14.0. HRMS $(ESI)^-$ m/z calcd for $C_{10}H_{20}NO_4^-$ ($[M-H]^+$) 218.1398; found 218.1408. The diastereomer ratio (dr) and enantiomeric purity (*ee*) were determined by HPLC analysis using a Chirapak IA (4.6 x 250 mm) using mobile phase of (2:98 *i*-propanol:*n*-hexane, flow rate of 1 mL/min at 25 °C, UV detection at 220 nm): *anti* diastereomer (*S*,*R*)-enantiomer: t_r = 76.80 min; *syn* diastereomer (*R*,*R*)-enantiomer: t_r = 80.29 min, (*S*,*S*)-enantiomer: t_r = 86.91 min.

(*anti*/*syn*)-1-Nitrotridecane-2,3-diol (14a and 14b): Following the general procedure for tandem *α*-aminooxylated-Henry reaction, the residue was purified by silica gel column chromatography using (EtOAc/hexane 1:5 v/v) as eluent to furnish the *anti*-**14a** and *syn*-**14b** diastereomers as white solid in 70% yield (182 mg, 0.70 mmol), (>99% *ee* for *anti*, 98% *ee* for *syn*) and as 3.30:1 *anti*:*syn* mixture of diastereomers. IR (CH_2Cl_2) *v*: 3520, 3123, 2933, 1596, 1582, 1562, 1518, 1472, 1379, 1279, 1232, 1115, 1072, 772 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) *δ*: 4.62-4.48 (m, 2H), 4.28-4.21 (m, 1H), 3.79-3.54 (m, 1H), 3.18 (s, 1H), 2.32 (s, 1H), 1.59-1.26 (m, 18H), 0.88 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 78.7, 77.2, 72.8, 71.8, 71.6, 70.8, 33.4, 32.6, 31.8, 29.5, 29.4, 29.4, 29.4, 29.2, 25.6, 25.4, 22.6, 14.0. HRMS $(ESI)^-$ m/z calcd for $C_{13}H_{26}NO_4^-$ ($[M-H]^+$) 260.1867; found 260.1872. The diastereomer ratio (dr) and enantiomeric purity (*ee*) were determined by HPLC analysis using a Chirapak IA (4.6 x 250 mm) using mobile phase of (5:95 *i*-propanol:*n*-hexane, flow rate of 1 mL/min at 25 °C, UV detection at 210 nm): *anti* diastereomer (*S*,*R*)-enantiomer: t_r = 17.51 min; *syn* diastereomer (*R*,*R*)-enantiomer: t_r = 22.03 min, (*S*,*S*)-enantiomer: t_r = 26.03 min.

(*anti*/*syn*)-1-Nitrotridecane-2,3-diol (14c and 14d): Following the general procedure for tandem *α*-aminooxylated-Henry reaction, the residue was purified by silica gel column chromatography using (EtOAc/hexane 1:5 v/v) as eluent to furnish the *anti*-**14c** and *syn*-**14d** diastereomers as off white solid in 65% yield (170 mg, 0.65 mmol), (70% *ee* for *anti*, 96% *ee* for *syn*) and as 1.10:1 *anti*:*syn* mixture of diastereomers. ^1H NMR (400 MHz, $CDCl_3$) *δ*: 4.63-4.49 (m, 2H), 4.29 (d, *J* = 5.04 Hz, 1H), 3.72-3.54 (m, 1H), 3.16 (br s, 1H), 1.58-1.24 (m, 18H), 0.85 (t, *J* = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 78.7, 77.2, 72.8, 71.8, 71.6, 70.5, 33.4, 32.6, 31.8, 29.5, 29.5, 29.4, 29.4, 29.3, 25.6, 25.4, 22.6, 14.1. The above *anti*-/*syn*-diastereomers **14** were separated and purified by silica gel column chromatography to furnish the *anti*-**14c** (99% *ee*) and *syn*-**14d** (99% *ee*) diastereomers as white solid. The diastereomer ratio (dr) and enantiomeric purity (*ee*) were determined by HPLC analysis using a Chirapak IA (4.6 x 250 mm) using mobile phase of (5:95 *i*-propanol:*n*-hexane, flow rate of 1 mL/min at 25 °C, UV detection at 210 nm): *anti* diastereomer (*S*,*R*)-enantiomer: t_r = 17.41 min, (*R*,*S*)-enantiomer: t_r = 19.40 min; *syn* diastereomer (*R*,*R*)-enantiomer: t_r = 22.18 min, (*S*,*S*)-enantiomer: t_r = 26.17 min.

(*anti*/*syn*)-1-Nitrooctadecane-2,3-diol (15a and 15b): Following the general procedure for tandem *α*-aminooxylated-Henry reaction, the residue was purified by silica gel column chromatography using (EtOAc/hexane 1:5 v/v) as eluent to furnish the *anti*-**15a** and *syn*-**15b** diastereomers as white solid in 68% yield (225 mg, 0.68 mmol), (80% *ee* for *anti*, >99% *ee* for *syn*) and as 1.20:1 *anti*:*syn* mixture of diastereomers. IR (CH_2Cl_2) *v*: 3591, 3586, 2931, 1632, 1575, 1532, 1474,

1362, 1186, 1085, 773 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 4.62-4.48 (m, 2H), 4.26-4.23 (m, 1H), 3.78-3.55 (m, 1H), 2.96 (br s, 1H), 2.10 (br s, 1H), 1.60-1.25 (m, 28H), 0.88 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 78.6, 77.2, 72.8, 71.7, 71.6, 70.7, 33.5, 32.7, 31.9, 29.6, 29.6, 29.5, 29.4, 29.4, 29.3, 25.6, 25.4, 22.6, 14.1. HRMS $(ESI)^+$ m/z calcd for $C_{18}H_{38}NO_4^+$ ($[M+H]^+$) 332.2796; found 332.2798. The diastereomer ratio (dr) and enantiomeric purity (*ee*) were determined by HPLC analysis using a Chirapak IA (4.6 x 250 mm) using mobile phase of (3:97 *i*-propanol:*n*-hexane, flow rate of 1 mL/min at 25 °C, UV detection at 220 nm): *anti* diastereomer (*S*,*R*)-enantiomer: t_r = 37.04 min, (*R*,*S*)-enantiomer: t_r = 42.21 min; *syn* diastereomer (*R*,*R*)-enantiomer: t_r = 28.16 min, (*S*,*S*)-enantiomer: t_r = 32.99 min.

(*anti*/*syn*)-1-Nitrooctadecane-2,3-diol (15c and 15d): Following the general procedure for tandem α-aminooxylated-Henry reaction, the residue was purified by silica gel column chromatography using (EtOAc/hexane 1:5 v/v) as eluent to furnish the *anti*-**15c** and *syn*-**15d** diastereomers as off white solid in 67% yield (220 mg, 0.67 mmol), (86% *ee* for *anti*, 97% *ee* for *syn*) and as 1.64:1 *anti*:*syn* mixture of diastereomers. ^1H NMR (400 MHz, $CDCl_3$) δ: 4.60-4.46 (m, 2H), 4.24-4.21 (m, 1H), 3.77-3.53 (m, 1H), 2.94 (br s, 1H), 1.58-1.23 (m, 28H), 0.86 (t, J = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 78.3, 76.9, 72.4, 71.4, 71.3, 70.4, 33.2, 32.4, 31.5, 29.3, 29.3, 29.2, 29.1, 29.1, 29.0, 25.3, 25.1, 22.3, 13.8. The diastereomer ratio (dr) and enantiomeric purity (*ee*) were determined by HPLC analysis using a Chirapak IA (4.6 x 250 mm) using mobile phase of (3:97 *i*-propanol:*n*-hexane, flow rate of 1 mL/min at 25 °C, UV detection at 220 nm): *anti* diastereomer (*S*,*R*)-enantiomer: t_r = 36.93 min, (*R*,*S*)-enantiomer: t_r = 42.07 min; *syn* diastereomer (*R*,*R*)-enantiomer: t_r = 28.04 min, (*S*,*S*)-enantiomer: t_r = 32.37 min.

(2*S*,3*S*)-1-Nitrooctadecane-2,3-diol (15d): The above *anti*-/*syn*-diastereomers **15** (220 mg) were separated and purified by silica gel column chromatography using (EtOAc/hexane 1:9 v/v) as eluent to furnish the *syn*-**15d** diastereomer as white solid in 25% yield (84 mg, 0.25 mmol) with 98% *ee*. $[\alpha]_D^{25}$ +35.2 (*c* 0.2, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ: 4.60-4.49 (m, 2H), 4.27-4.18 (m, 1H), 3.75-3.72 (m, 1H), 2.38 (br s, 2H), 1.59-1.40 (m, 2H), 1.37-1.20 (m, 26H), 0.88 (t, J = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 77.2, 72.8, 71.7, 32.7, 31.9, 29.6, 29.5, 29.4, 29.3, 25.6, 22.6, 14.1. The enantiomeric purity (*ee*) was determined by HPLC analysis using a Chirapak IA (4.6 x 250 mm) using mobile phase of (3:97 *i*-propanol:*n*-hexane, flow rate of 1 mL/min at 25 °C, UV detection at 220 nm): (*R*,*R*)-enantiomer: t_r = 29.88 min, (*S*,*S*)-enantiomer: t_r = 32.64 min.

(2*R*,3*S*)-1-Nitrooctadecane-2,3-diol (15c): After separation of the *syn*-**15d** diastereomer, the *anti*-**15c** diastereomer was quickly eluted (EtOAc/hexane 1:5 v/v) as white solid in 42% yield (136 mg, 0.42 mmol) with 99% *ee*. $[\alpha]_D^{25}$ +48.7 (*c* 1, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ: 4.63-4.48 (m, 2H), 4.26-4.22 (m, 1H), 3.59-3.55 (m, 1H), 1.64-1.48 (m, 2H), 1.42-1.21 (m, 26H), 0.88 (t, J = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 78.6, 71.7, 70.7, 33.5, 31.9, 29.6, 29.5, 29.4, 29.4, 29.3, 25.4, 22.6, 14.1. The enantiomeric purity (*ee*) was determined by HPLC analysis using a Chirapak IA (4.6 x 250 mm) using mobile phase of (3:97 *i*-propanol:*n*-hexane, flow rate of 1 mL/min at 25 °C, UV detection at 220 nm): (*S*,*R*)-enantiomer: t_r = 38.68 min, (*R*,*S*)-enantiomer: t_r = 43.44 min.

Ethyl (2*S*,3*S*)-2,3-dihydroxyoctadecanoate (26): A solution of *anti*-**15c** diastereomer (300 mg, 0.91 mmol), sodium nitrite (190 mg, 2.73 mmol), and acetic acid (0.54 mL, 9.1 mmol) in dimethyl sulfoxide (2 mL) was stirred at 35 °C for 24 h. The reaction mixture was then diluted with water, acidified with 10% aqueous solution of hydrochloric acid (10 mL), extracted with ether (3 x 50 mL), dried over anhydrous Na_2SO_4, concentrated *in vacuo*, and used as such for the next step without further purification. To an ethanolic (4.0 mL) solution of above crude was added chlorotrimethylsilane (230 µL, 1.82 mmol) at room temperature and stirred for 12 h. The reaction mixture was then concentrated on a rotary evaporator and purified by silica gel column chromatography using (EtOAc/hexane 1:4 v/v) as eluent to afford the diol ester **26** (200 mg, 64%) as white solid. $\{[\alpha]_D^{25}$ -13.8 (*c* 0.5, CH_2Cl_2); IR (CH_2Cl_2) *v*: 3551, 3349, 1731, 775 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 4.29 (q, J = 6.8, 14.2 Hz, 2H), 4.08 (d, J = 1.84 Hz, 1H), 3.90-3.86 (m, 1H), 1.63-1.58 (m, 2H), 1.49-1.25 (m, 29H), 0.88 (t, J = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 173.7, 72.9, 62.1, 72.5, 33.8, 31.9, 29.6, 29.6, 29.5, 29.5, 29.4, 29.3, 25.7, 22.6, 14.1; HRMS $(ESI)^+$ m/z calcd for $C_{20}H_{41}O_4^+$ ($[M+H]^+$) 345.3000; found 345.2998.

Ethyl (4*S*,5*S*)-5-pentadecyl-1,3,2-dioxathiolane-4-carboxylate 2-oxide (27): To a stirred solution of diol **26** (200 mg, 0.58 mmol) in dry CH_2Cl_2 (5 mL) were added Et_3N (160 µL, 1.16 mmol) and $SOCl_2$ (51 µL, 0.696 mmol) at 0 °C over a period of 10 min. The reaction mixture was then stirred for 1 h at 0 °C, quenched by adding water and extracted with CH_2Cl_2. The organic layer was separated, washed with water followed by brine, dried over Na_2SO_4, concentrated and purified by silica gel column chromatography using (EtOAc/hexane 1:19 v/v) as eluent to afford the sulfite ester **27** (215 mg, 95%) as yellow oil. $\{[\alpha]_D^{25}$ -31.2 (*c* 1, CH_2Cl_2); IR (CH_2Cl_2) *v*: 1767, 1735, 1261, 723 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 5.12-5.08 (m, 1H), 4.49 (d, J = 7.8 Hz, 1H), 4.34-4.27 (m, 2H), 1.57-1.22 (m, 31H), 0.88 (t, J = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 167.3, 82.6, 81.4, 62.5, 32.4, 31.9, 29.6, 29.5, 29.5, 29.4, 29.3, 29.2, 25.2, 22.6, 14.1, 14.0; HRMS $(ESI)^+$ m/z calcd for $C_{20}H_{39}O_5S^+$ ($[M+H]^+$) 391.2513; found 391.2511.

Ethyl (2*R*,3*S*)-2-azido-3-hydroxyoctadecanoate (28): To a solution of cyclic sulfite **27** (200 mg, 0.51 mmol) in dry DMF (5 mL) was added NaN_3 (100 mg, 1.53 mmol) under argon. The reaction mixture was stirred at 80 °C for 12 h under argon. The reaction mixture was diluted with water, extracted with ether (3 x 100 mL), dried over Na_2SO_4, concentrated and purified on a silica gel column chromatography using (EtOAc/hexane 1:40 v/v) as eluent to give azido ester **28** (166 mg, 91%) as white solid. $\{[\alpha]_D^{25}$ -43.1 (*c* 1.1, CH_2Cl_2); IR (CH_2Cl_2) *v*: 3621, 2108, 1733, 735 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 4.32-4.26 (m, 2H), 3.95-3.90 (m, 2H), 1.58-1.50 (m, 2H), 1.37-1.21 (m, 29H), 0.88 (t, J = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 168.9, 71.9, 66.1, 62.0, 33.0, 31.9, 29.6, 29.5, 29.5, 29.4, 29.3, 29.3, 25.3, 22.6, 14.1, 14.1; HRMS $(ESI)^+$ m/z calcd for $C_{20}H_{40}N_3O_3^+$ ($[M+H]^+$) 370.3064; found 370.3065.

(-)-L-*threo*-Sphinganine (Safingol) (21): To a freshly distilled THF (5 mL) solution of $LiAlH_4$ (70 mg, 1.8 mmol) at 0 °C was added a solution of azido ester **28** (120 mg, 0.3 mmol) in 5 mL THF. After stirring the reaction mixture for 5 min, ice-cooled bath was removed and stirred the reaction mixture at 70 °C for 12 h until the full consumption of the azido ester (monitored by TLC). The reaction mixture was then diluted with 10 mL of dry THF and filtered through a pad of silica gel slurry in hexane in a sintered glass funnel to remove the impurities by gentle suction. The silica pad was washed with a mixture of $CHCl_3$/MeOH (1:4 v/v), dried over Na_2SO_4, concentrated and purified by silica gel column chromatography using ($CHCl_3$/MeOH/NH_4OH 32:6:1) as eluent to give the target L-*threo*-sphinganine (safingol) **21** (73 mg, 81%) as white solid. $\{[\alpha]_D^{25}$ -23.5 (*c* 0.5, $CHCl_3$/MeOH 3:1) $\{[\alpha]_D^{25}$ -7.5 (*c* 0.09, C_2H_5OH) [Lit.[10a] -7.6 (*c* 0.09, C_2H_5OH)]; IR (MeOH) *v*: 3623, 3425, 1565, 756 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 3.86-3.83 (m, 1H), 3.71-3.61 (m, 2H), 2.56 (br s, 4H), 1.46-1.12 (m, 28H), 0.88 (t, J = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 75.2, 62.6, 61.9, 34.1, 31.8, 30.2, 29.8, 29.6, 29.3, 29.2, 22.6, 14.0. HRMS $(ESI)^+$ m/z calcd for $C_{18}H_{40}NO_2^+$ ($[M+H]^+$) 302.3054; found 302.3035.

Acknowledgements

S.K.P. is thankful to Department of Science and Technology, New Delhi, for generous funding of the project (Grant No. EMR/2016/003649). Y.G. and R.K. thank UGC, New Delhi for SRF and JRF, respectively.

Keywords: tandem• α-aminoxylation• Henry reaction• β,γ-dihydroxynitroalkane• tetrahydrosalen

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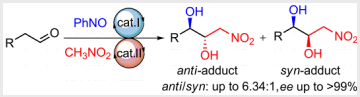
Entry for the Table of Contents

Full Paper

A novel and rapid asymmetric syntheses of 1,2-diol derivatives *anti*- and *syn*-β,γ-dihydroxynitroalkanes *via* organocatalyzed tandem α-aminooxylation-Henry reactions are described. The targeted diol derivatives are synthesized in good yields, with excellent enantio- and low to moderate diasteroselectivities under mild conditions. Synthesis of an antineoplastic and antipsoriatic drug (-)-L-*threo*-sphinganine demonstrate the synthetic utility of the fragments generated in the title reaction.



*Yuvraj Garg, Ramandeep Kaur and Satyendra Kumar Pandey**

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Organocatalytic Asymmetric Tandem *α*-Aminooxylation-Henry Reactions for the Synthesis of 1,2-Diols: Total Synthesis of (-)-L-*threo*-Sphinganine

Key words:α-aminooxylation, Henry reaction