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# Synthesis of *N*-Substituted Iminosugar Derivatives and Evaluation of Their Immunosuppressive Activities

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Supporting information for this article is available on the WWW under http://www.chemmedchem.org or from the author.

**Abstract:** It is important to find more effective and safer immunosuppressants because the clinically-used immunosuppressive agents have significant side-effects. A series of *N*-substituted iminosugar derivatives were designed and synthesized, and their immunosuppressive effects were evaluated by CCK-8 assay. The results revealed that iminosugars **10e** and **10i** exhibited the strongest inhibitory effect on mouse splenocyte proliferation ($IC_{50}$ = 2.16 and 2.48 μM, respectively), whereas the iminosugars containing an amide group near the hydrophilic head (compounds **10j**-**n**) exhibited no inhibitory effects. Further studies revealed that the inhibitory effects on splenocyte proliferation may come from the suppression of both IFN-γ and IL-4 cytokines. Our results suggested that the synthetic iminosugars, especially compounds **10e** and **10i** hold the potential as immunosuppressive agents.

## Introduction

Inhibition of the acute rejection is the key to the success of organ transplantation.[1] Although the use of immunosuppressive agents has greatly improved the transplant survival, the current immunosuppressants such as cyclosporin A (CSA), tacrolimus, mycophenolate mofetil, and sirolimus, have significant side-effects including nephrotoxicity, neurotoxicity, infection, cancer, new onset post-transplant diabetes mellitus, hyperlipidemia, and hypertension.[2] Therefore, it is urgent to find more effective and safer immunosuppressants.

Iminosugars are carbohydrate mimetics in which the endocyclic oxygen of sugar ring is replaced by nitrogen. Because of their structural similarity to sugars, iminosugars can act as potent inhibitors for a variety of carbohydrate-processing enzymes involved in important biological events,[3] hence, they possess a range of biological activities that spin a wide cross section of diseases such as tumor metastasis,[4] diabetes,[5] viral infections[6] and lysosomal storage disorders.[7] The broad biological activities of iminosugars have aroused many efforts in the synthesis of iminosugars and their derivatives.[8] Some iminosugars have been already approved as drugs on the market, for example, Glyset™ and Zavesca™, for the treatment of noninsulin-dependent diabetes and Gaucher's disease, respectively. However, the use of iminosugar derivatives as immunosuppressive agents is an area that is less explored. To date, only castanospermine (Figure 1, 1), a naturally-occurring indolizidine alkaloid (bicyclic iminosugar), has been found to exhibit some immunosuppressive activity and prolong heart allograft survival in rats.[9] In recent years, our group has been actively involved in search of iminosugar derivatives with immunomodulating activities. By a series of structural modifications on iminosugars, such as alteration in the configuration of the hydroxyl group, *N*-alkylation and *N*-arylation, several synthetic monocyclic iminosugar derivatives (Figure 1, **2**–**6**) with good immunosuppressive activities both in vitro[10] and in vivo[11] have been identified. Among them, *N*-decyl-1,4-dideoxy-l,4-iminotetritol (Figure 1, **5**) displayed immunosuppressive activities in vitro and prolonged the allograft survival in the mouse skin transplantation experiment.

Recently, spingosine-1-phosphate receptor 1 ($S1P_1$) has been actively pursued as an important therapeutic target due to its essential role in immune regulation.[12] One of the $S1P_1$ modulators, Fingolimod (FTY720/Gilenya; Novartis) (Figure 1, **7**), was approved for the treatment of relapsing multiple sclerosis in 2010.[13] Interestingly, modifications of the carbon chain in **7** resulted in different immune responses and the selectivity between $S1P_1$ and $S1P_3$. KRP-203 (Figure 1, **8**), an analogue of FTY720, is a more selective agonist of the S1P1 receptor and is believed to be safer than FTY720,[14] thus holding the great potential in the treatment of autoimmune diseases and in the prevention of transplant rejection. Compound **9** is another selective $S1P_1$ agonist. Compared with FTY720, compound **9** exerted good lymphopenia activity in vivo but with weak influence on heart rate.[15] KRP-203, compound **9**, and FTY720 have some common structural characteristics: they all possess the same hydrophilic 2-aminopropane-1,3-diol fragment and a hydrophobic tail.

Inspired by these observations, to find iminosugars with better activities and to further understand the structure–activity relationships (SARs) of this type of compounds, we report herein the synthesis of several *N*-alkylated iminosugar derivatives and the evaluation of their immunosuppressive activities.

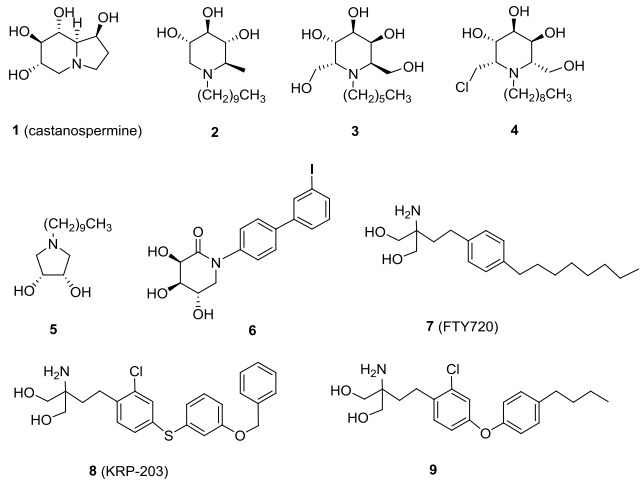



**Figure 1.** Structures of some immunoregulatory molecules

## Results and Discussion

### Design

Fourteen *N*-alkylated 1,4-dideoxy-l,4-iminotetritol derivatives with side chains containing one or more phenyl or biphenyl groups (Figure 2, compounds **10a**-**n**) were designed. Since FTY720, KRP-203, and compound **9** have the same 2-aminopropane-1,3-diol structure, we want to explore whether the substitution of this polar head group with a conformation-locking iminosugar (1,4-dideoxy-l,4-iminotetritol) would improve the immunosuppressive activity. To further investigate whether the *N*-alkylated side chain influences the immunosuppressive activity or not, various side chains based on the reported immunoregulatory molecules are chosen. All these target compounds could be prepared by coupling compound **11** with a variety of alkyl bromides **17a**-**n** (Figure 2).

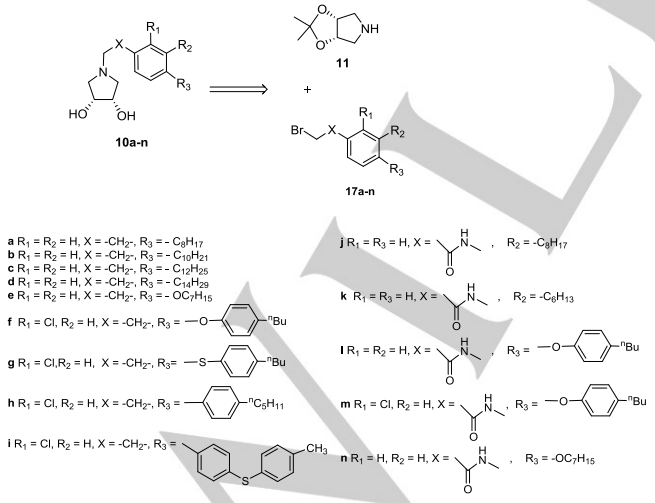
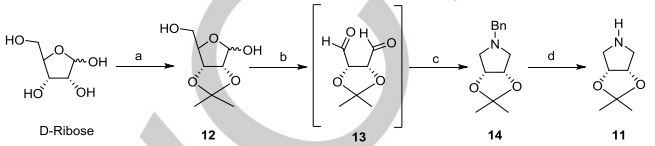



**Figure 2.** Structures of the designed iminosugars with alkyl chains inserted phenyl or biphenyl groups.

### Chemistry

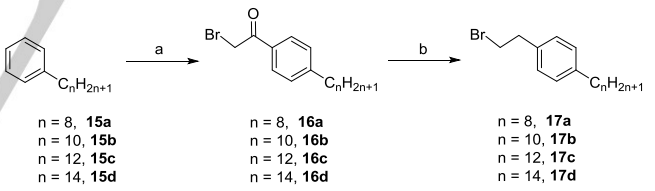
The preparation of the key iminosugar intermediate **11** is shown in Scheme 1. The reaction of D-ribose with acetone in the presence of a catalytic amount of iodine produced isopropylidene-D-ribose (**12**) in 84% yield.[16] After oxidation of **12** by $NaIO_4$, the unstable aldehyde **13** was immediately subjected to reductive amination, leading to the formation of benzylated iminosugar **14** in 86% yield over two steps. Subsequently, the catalytic hydrogenolysis of **14** yielded compound **11**, which was directly used for the next step without further purification.[17]



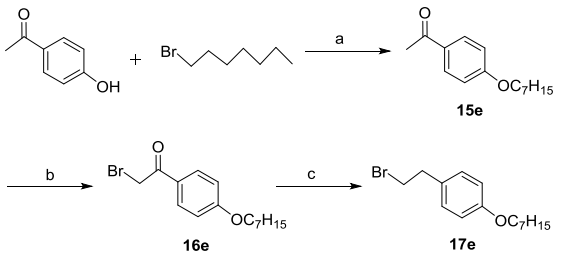

**Scheme 1**. Synthesis of iminosugar **11**. Reagents and conditions: (a) acetone/$I_2$, overnight, 84% yield; (b) $NaIO_4$, $H_2O$, 20 h; (c) $BnNH_2$, $NaBH_3CN$/MeOH, 3 Å MS, 2 h, 86% yield over two steps; (d) $Pd(OH)_2$/C (20% Pd), $H_2$, MeOH, 48 h.

Bromides **17a**–**d** were obtained by Friedel−Crafts acylation of **15a**–**d** with bromoacetyl bromide[18] followed by reduction of the carbonyl group with dimethylamine-borane in the presence of titanium tetrachloride (Scheme 2).[19]

Compound **17e** was prepared as outlined in Scheme 3. *p*-Hydroxyacetophenone was first alkylated using *n*-heptyl bromide in the presence of $K_2CO_3$ in DMF (70 °C), and then the obtained phenyl ether **15e** was subjected to radical bromination with $CuBr_2$/EtOAc, affording the desired bromoacetophenone **16e**.[20] Reduction of the carbonyl group in **16e** provided compound **17e**.




**Scheme 2**. Synthesis of **17a-d**. Reagents and conditions: (a) bromoacetyl bromide, $AlCl_3$, $CH_2Cl_2$, 3-5 h, 96-99% yield; (b) $Me_2NH{\cdot}BH_3$, $TiCl_4$, $CH_2Cl_2$, overnight, 96-97% yield.

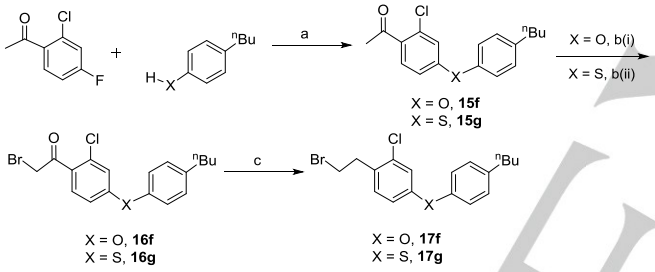



**Scheme 3**. Synthesis of **17e**. Reagents and conditions: (a) $K_2CO_3$, DMF, 70 °C, 9 h, 98% yield; (b) $CuBr_2$, EtOAc, reflux, overnight; (c) $Me_2NH{\cdot}BH_3$, $TiCl_4$, $CH_2Cl_2$, overnight, 85% yield over two steps.

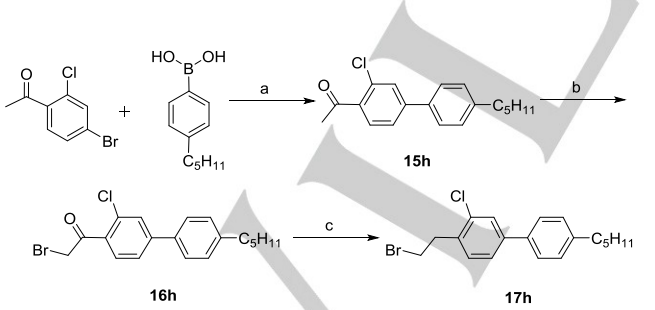
As shown in Scheme 4, compounds **17f** and **17g** were prepared through the intermediates **15f** and **15g** that were obtained by the aromatic nucleophilic substitution reaction of 2-chloro-4-fluoro-acetophenone with *p*-(*n*-butyl)phenol or *p*-(*n*-butyl)thiophenol. The radical bromination of compounds **15f** and **15g** with NBS/*p*-TsOH[21] and $CuBr_2$/EtOAc provided compounds **16f** and **16g**, respectively. Reduction of the carbonyl group by dimethylamine-borane/titanium tetrachloride afforded **17f** and **17g**.

The biphenyl compound **17h** was synthesized from 2-chloro-4-bromo-acetophenone through Suzuki coupling reaction,[22] followed by NBS bromination and reduction (Scheme 5).

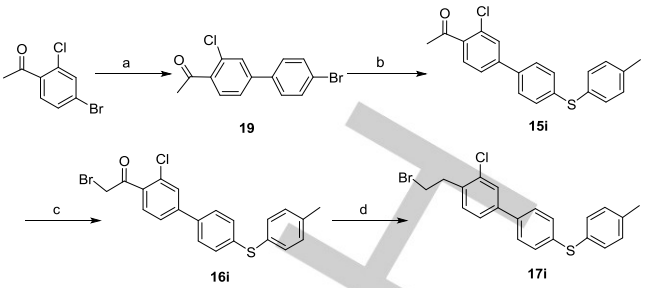
The synthesis of diaryl sulfide **17i** was described in Scheme 6. The palladium-mediated Suzuki coupling between 2-chloro-4-bromo-acetophenone and 1-bromo-4-iodobenzene afforded biphenyl bromide **19**. The bromide **19** was converted to the diaryl sulfide **15i** by a coupling reaction using 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene as the phosphine ligand,[23] which was followed by bromination and reduction, affording compound **17i.**




**Scheme 4**. Synthesis of **17f** and **17g**. Reagents and conditions: (a) $K_2CO_3$, DMF, 115 °C, 5 h to overnight, yield: 100% for **15f**, 85% for **15g**; (b) (i) NBS, *p*-TsOH, MeCN, 50 °C, overnight; (ii) $CuBr_2$, EtOAc, reflux, overnight; (c) $Me_2NH{\cdot}BH_3$, $TiCl_4$, $CH_2Cl_2$, overnight, for **17f**: 72% yield over two steps, for **17g**: 51% yield over two steps.

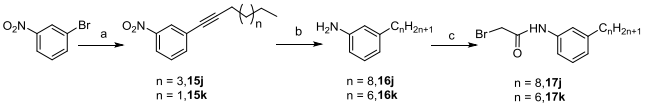



**Scheme 5**. Synthesis of **17h**. Reagents and conditions: (a) $Pd(PPh_3)_4$, $NaHCO_3$, DME/$H_2O$, 65 °C, 4 h, quantitative; (b) NBS, *p*-TsOH, MeCN, 50 °C, overnight; (c) $Me_2NH{\cdot}BH_3$, $TiCl_4$, $CH_2Cl_2$, overnight, 47% yield over two steps.

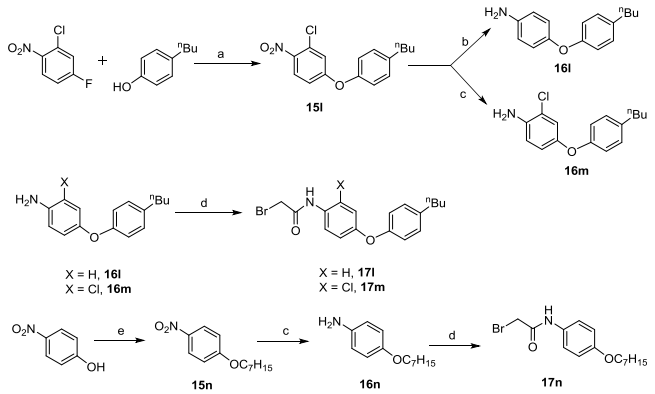



**Scheme 6**. Synthesis of **17i**. Reagents and conditions: (a) (i) bis(pinacolate)diboron, $PdCl_2(Cy_3P)_2$, AcOK, dioxane, 100 °C; (ii) 1-bromo-4-iodobenzene, $Pd(PPh_3)_4$, $NaHCO_3$, DME/$H_2O$, 100 °C, 53% yield over two steps; (b) *p*-toluene thiophenol, Xantphos, $Pd_2(dba)_3{\bullet}CHCl_3$, DIPEA, dioxane, reflux, 87% yield; (c) $CuBr_2$, EtOAc, reflux, overnight; (d) $Me_2NH{\cdot}BH_3$, $TiCl_4$, $CH_2Cl_2$, overnight, 57% yield over two steps.

A preliminary exploration of S1P related structures has demonstrated that an amide insertion in the S1P structure is well tolerated.[24] Clemens and co-workers also demonstrated that replacing the ethylene component of FTY720 with an amide bond allowed for active molecules across S1P receptor subtypes 1, 3, 4, and 5.[25] As a useful reference for the structure-activity relationship (SAR) studies, the compounds **17j**-**n** incorporating an amide bond between the phenyl ring and the methylene were needed. As shown in Scheme 7, 3-bromonitrobenzene was treated with 1-octyne/ 1-hexyne in a Sonogashira cross-coupling reaction[26] to furnish **15j**/**15k** in high yield. The nitro and alkyne groups were then reduced by hydrogen using palladium on charcoal to provide 3-octylaniline/3-hexylaniline (**16j**/**16k**).[27] When we tried to reduce the nitro group to amino group by catalytic hydrogenation, the chlorine atom in compound **15l** (Scheme 8) was also reduced to produce compound **16l**. However, the zinc powder reduction could provide the desired product without affecting the chlorine atom. The anilines obtained were subsequently treated with 2-bromoacetyl bromide in the presence of triethylamine in dichloromethane to give compounds **17j**-**n**.

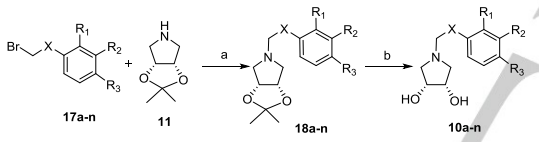



**Scheme 7**. Synthesis of **17j** and **17k**. Reagents and conditions: (a) 1-octyne or 1-hexyne, $[Pd(PPh_3)_2Cl_2]$, CuI, $Et_3N$, 99% yield; (b) $H_2$ (g), Pd/C, MeOH; (c) bromoacetyl bromide, $Et_3N$, $CH_2Cl_2$, overnight; for **17j**:36% yield over two steps; for **17k**: 58% yield over two steps.



**Scheme 8**. Synthesis of **17l-n**. Reagents and conditions: $K_2CO_3$, DMF, 70 °C, 9 h, 100% yield; (b) $H_2$ (g), Pd/C, MeOH, overnight; (c) Zn, $NH_4Cl$, MeOH, 45 °C, 8-10 h; (d) bromoacetyl bromide, $Et_3N$, $CH_2Cl_2$, overnight; for **17l**: 76% yield over two steps; for **17m**: 90% yield over two steps; for **17n**: 65% yield over two steps; (e) 1-bromoheptane, $K_2CO_3$, DMF, 70 °C, 6 h, 80% yield.

With all substrates in hand, the coupling reaction was performed. As shown in Scheme 9, the coupling reaction between iminosugar **11** and the substituted alkyl bromides **17a**-**n** proceeded smoothly in acetonitrile in the presence of potassium carbonate, affording compounds **18a**-**n** in 21-98% yields. Finally, the acid-catalyzed deprotection of acetonide in **18a**–**n** led to the target compounds **10a**–**n** in 71–90% yields.



**Scheme 9**. Synthesis of the target compounds **10a**-**n**. Reagents and conditions: (a) $K_2CO_3$, MeCN, 50 °C, overnight; (b) 6 M HCl, MeOH, $H_2O$, 50 °C.

## Biology

With compounds **10a**–**n** in hand, their effects on Con A-induced mouse splenocytes proliferation were assessed by the cell counting kit-8 (CCK-8) assay,[10a] by which the mitochondrial dehydrogenase activity of the surviving cells was measured. The mouse splenocytes were induced by 5 μg $mL^{-1}$ of Con A and were cultured in RPMI-1640 medium. After inoculated in 96-well plates at about $5\times10^5$ cells per well, the cells were treated with 5 μM concentration of iminosugars **10a**-**n** at 37 °C and 5% $CO_2$ for 48 h. The Con A-treated splenocytes were used as the control and cyclosporine A (CSA, 1 μM, 95.52% inhibitory rate) treated splenocytes were used as the positive control. The inhibitory rates of all compounds were shown in Figure 3. Compared with the control, none of the iminosugars containing an amide group near the hydrophilic head (compounds **10j**-**n**) exhibited inhibitory effects on mouse splenocyte proliferation. The levels of cell proliferation were reduced by 71.90%, 67.60%, 61.40%, 87.18%, 66.14%, 72.54%, 88.37% when including 5 μM of compounds **10a**, **10b**, **10c**, **10e**, **10g**, **10h**, **10i** respectively. Among these compounds with inhibitory activities, **10e** (87.18%) and **10i** (88.37%) exhibited strong inhibitory effects. Comparing compounds **10a** (71.90%), **10b** (67.60%), **10c** (61.40%), **10d** (39.54%) with **5** (57.59%), it seemed that insertion of a phenyl ring into the alkyl chain of **5** would improve the inhibitory activity, but the inhibitory rate was decreased gradually with the increase of the carbon numbers of the linear alkyl chain on the benzene ring. When the flexible alkyl tail was linked to the benzene ring by an oxygen atom (compound **10e**), the inhibitory rate showed an enormous leap (87.18%). Thus, to check if the introduction of another benzene ring would influence the inhibitory activities, compounds **10f-i** were prepared. The experimental data revealed that the inhibitory activity of **10f** and **10g** was even weaker than that of **10a**, but the introduction of a biphenyl moiety into the hydrophobic part was beneficial to enhancement of the immunosuppressive activity and compound **10i** showed the strongest inhibitory effect (88.37% at 5 μM). The 50% inhibitory concentrations ($IC_{50}$) of compounds **10a**, **10b**, **10c**, **10e**, **10g**, **10h**, **10i** were further tested and the results were summarized in Table 1. Iminosugars **10e** and **10i** showed promising inhibitory activity, with $IC_{50}$ values of 2.16 μM and 2.48 μM, respectively.

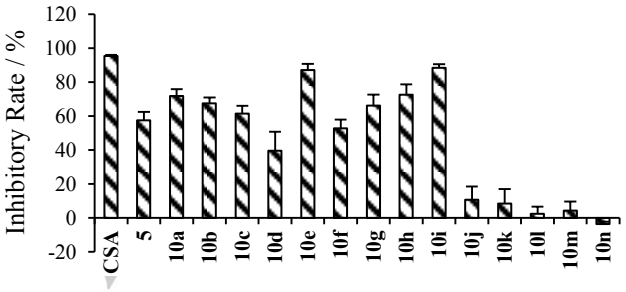



**Figure 3**. Effects of compounds **10a**-**n** on Con A-induced mouse splenocytes proliferation were assessed by the CCK-8 assay. Concentration of CSA was 1 μM and concentration of compounds **10a**-**n** was 5 μM. Data are means ± SEM of at least three independent experiments.

**Table 1**. $IC_{50}$ determination of compounds **10a**, **10b**, **10c**, **10e**, **10g**, **10h**, **10i** against mouse splenocytes proliferation

| Compound | Inhibition of mouse splenocytes proliferation $IC_{50}$ [μM] |
|---|---|
| **10a** | 2.34 (±0.63) |
| **10b** | 2.59 (±0.53) |
| **10c** | 3.61 (±0.46) |
| **10e** | 2.16 (±0.24) |
| **10g** | 3.06 (±0.22) |
| **10h** | 3.53 (±0.08) |
| **10i** | 2.48 (±0.16) |

To further confirm the immunosuppressive activity of these compounds, a cytokine-secretion assay was employed.[27] The mouse splenocytes induced by Con A were incubated with 5 μM of compounds **10a**, **10b**, **10c**, **10e**, **10g**, **10h**, **10i** at 37 °C and 5% $CO_2$ for 72 h. The secretion of IFN-γ and IL-4 was detected from the supernatant of spleen cells using mice IFN-γ and IL-4 ELISA kits, respectively. The data were shown in Figure 4A and Figure 4B. All of these seven compounds showed inhibition to the IFN-γ secretion. As compared with the control, the level of

IFN-γ secretion was reduced by 42.44%, 57.57%, 58.59%, 50.53%, 46.73%, 65.97% and 73.13% when including 5 μM of compounds **10a**, **10b**, **10c**, **10e**, **10g**, **10h** and **10i**, respectively (Figure 4A, 102.93% for CSA at 1 μM). It was found that among these compounds, compounds **10b**, **10c**, **10h** and **10i** displayed obvious inhibitory effects on the release of cytokine IFN-γ. The assay on secretion of IL-4 from mice splenocytes was similar to that of IFN-γ (Figure 4B). As compared with the control, the level of IL-4 secretion was decreased by 64.91%, 58.11%, 40.18%, 85.04%, 79.03%, 78.07% and 98.31% when using 5 μM of compounds **10a**, **10b**, **10c**, **10e**, **10g**, **10h** and **10i**, respectively (Figure 4B, 105.81% for CSA at 1 μM). Compound **10i** showed the best inhibition effect on the secretion of both IFN-γ and IL-4. Compounds **10b**, **10h** and **10i** did not show significant inhibition selectivity between IL-4 and IFN-γ secretion. Compounds **10a**, **10e** and **10g** showed moderate inhibitory selectivity for IL-4 over IFN-γ secretion. Compound **10c** showed moderate inhibitory selectivity for IFN-γ over IL-4 secretion.

IFN-γ and IL-4 are the hallmark cytokines of Th1 and Th2 cells, respectively. Th1 and Th2 cells are two subclasses of T-helper cells. Th1 cells secret pro-inflammatory cytokines such as IFN-γ, IFN-β, and IL-2l; their responses predominate in organ-specific autoimmune disorders, acute allograft rejection, and in some chronic inflammatory disorders. Th2 cells produce cytokines such as IL-4, IL-5, and IL-6; their responses predominate in Omann's syndrome, transplantation tolerance, chronic graft-versus-host disease, systemic sclerosis, and allergic diseases. The cytokines that are secreted by Th1 cells (e.g. IFN-γ) primarily act in cell-mediated response, whereas those that are secreted by Th2 cells (e.g. IL-4) mainly function in B-cell activation and humoral response.[28] From the assay of the cytokine secretion, it seems that compound **10i** suppress both Th1 and Th2 cells. Therefore, it might show inhibitory activity toward both humoral response and cell-mediated immune response, holding the potential to treat different kinds of immune diseases. Besides, compound **10e** showed moderate inhibitory selectivity toward Th2 cells.

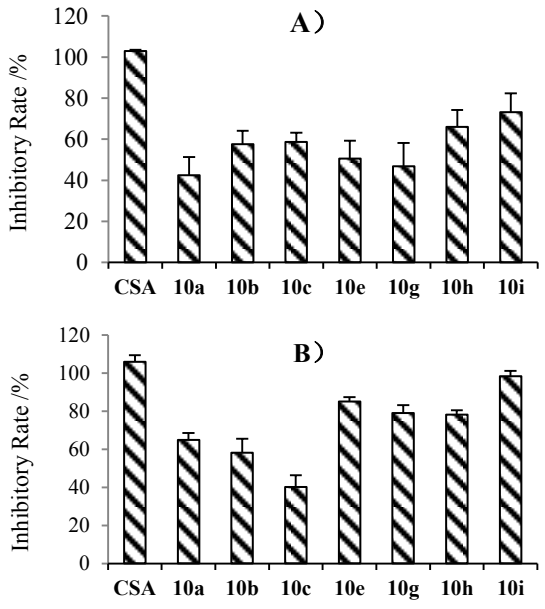



**Figure 4**. A) Inhibitory rates of compounds **10a**, **10b**, **10c**, **10e**, **10g**, **10h**, **10i** on IFN-γ secretion. B) Inhibitory rates of compounds **10a**, **10b**, **10c**, **10e**, **10g**, **10h**, **10i** on IL-4 secretion. Concentration of CSA was 1 μM and concentration of each compound was 5 μM. Data are means ± SEM of at least three independent experiments.

## Conclusions

In summary, we report herein the design and synthesis of fourteen novel *N*-substituted iminosugar derivatives by using concise synthetic routes. All the synthetic compounds were evaluated in vitro for the immunosuppressive activities on Con A-induced proliferation of mouse splenocytes by the CCK-8 assay. The results demonstrated that iminosugars **10e** and **10i** exhibited the strongest inhibition effect ($IC_{50}$ = 2.16 and 2.48 μM, respectively), whereas the iminosugars containing an amide group near the hydrophilic head (compounds **10j**-**n**) exhibited no inhibitory effects on mouse splenocyte proliferation. Further studies revealed that the inhibitory effects on splenocyte proliferation may come from the suppression of both IFN-γ and IL-4 cytokines. Our results suggested that the synthetic iminosugars, especially compounds **10e** and **10i** hold the potential as immunosuppressive agents.

## Experimental Section

### Chemistry

**General method**. Solvents were dried according to standard methods. Analytical thin-layer chromatography (TLC) was carried out on 0.25 mm silica gel 60 $F_{254}$ plates (Merck), employing ultraviolet light and/or staining with ceric ammonium molybdate for visualization. Column chromatography was performed employing 200–300 mesh silica gel or C-18 reversed-phase silica gel (Merck). $^1$H NMR and $^{13}$C NMR spectra were recorded on Bruker AVANCE III-400 spectrometer at ambient temperature. Chemical shifts (in ppm) were referenced to the residual proton signal of the solvent. High resolution mass spectrometry (HRMS) was performed on Waters Xevo G2 QTof (ESI) or Bruker Solarix XR (ESI) or Agilent 7980A/5975B GCMS (EI).

**General procedure for Friedel−Crafts acylation** (taking 4-octyl-α-bromoacetophenone as an example). Aluminum chloride (126.7 mg, 0.95 mmol) and 1-phenyloctane (0.2 mL, 0.90 mmol) were dissolved in dry $CH_2Cl_2$ (1.5 mL) and cooled to −10 °C. Bromoacetyl bromide (78 μL, 0.90 mmol) was added dropwise, and the mixture was allowed to return to room temperature while stirring overnight. The mixture was slowly poured into ice-water (100 mL), and the aqueous phase was extracted with $CH_2Cl_2$ (3 × 10 mL). The combined organic layers were washed with saturated sodium bicarbonate solution (10 mL) and brine (10 mL), dried over $Na_2SO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (petroleum ether/ethyl acetate, 70:1) to give the product **16a** as a brown and highly viscous oil. Yield: 2.74 g (98%).

**General procedure for aromatic carbonyl reduction by dimethylamine borane/titanium tetrachloride**. The carbonyl compound (50 mmol) was dissolved in 50 mL of $CH_2Cl_2$, cooled to 0 °C, and treated under stirring with 50 mmol of $TiCl_4$ which was added by syringe through a septum. Dimethylamine-borane (100 mmol) in 25 mL of $CH_2Cl_2$ was added to the cold solution, and the mixture was allowed to warm to room temperature. Stirring was continued for 30 min. Thereafter 1N HCl was added for the destruction of excess reductant and hydrolysis. The organic layer was separated, and the aqueous layer was extracted with $CH_2Cl_2$ (2 × 10 mL). The combined organic layers were washed with saturated aqueous NaCl, dried over $Na_2SO_4$. The solvent was removed,

and the product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate, 150:1) to give the product.

**General procedure for removing isopropylidene protecting group**. The substrate was dissolved in a combined solvent of MeOH/6 M HCl (10:3), and the mixture was heated at 50 °C overnight. After TLC analysis showed the complete disappearance of the starting material, the mixture was cooled to room temperature and concentrated in vacuo, purified by column chromatography on silica gel ($CH_2Cl_2$/MeOH) to provide the final product.

**4-Octyl-α-bromoacetophenone** (**16a**). $^1$H NMR (400 MHz, $CDCl_3$) *δ* 7.90 (d, *J* = 8.2 Hz, 2H), 7.29 (d, *J* = 8.2 Hz, 2H), 4.44 (s, 2H), 2.67 (t, *J* = 7.6 Hz, 2H), 1.65-1.59 (m, 2H), 1.31-1.27 (m, 10H), 0.88 (t, *J* = 6.1 Hz, 3H). The spectral data are in accordance with the data reported in ref. 29.

**4-*n*-Decyl-α-bromoacetophenone** (**16b**). Yield: 97%. $^1$H NMR (400 MHz, $CDCl_3$) *δ* 7.91 (d, *J* = 8.2 Hz, 2H), 7.29 (d, *J* = 8.2 Hz, 2H), 4.44 (s, 2H), 2.67 (t, *J* = 7.6 Hz, 2H), 1.65-1.59 (m, 2H), 1.31-1.26 (m, 14H), 0.88 (t, *J* = 6.6 Hz, 3H).

**4-*n*-Dodecyl-α-bromoacetophenone** (**16c**). Yield: 99%. $^1$H NMR (400 MHz, $CDCl_3$) *δ* 7.91 (d, *J* = 8.3 Hz, 2H), 7.29 (d, *J* = 8.2 Hz, 2H), 4.44 (s, 2H), 2.67 (t, *J* = 7.6 Hz, 2H), 1.67-1.59 (m, 2H), 1.32-1.25 (m, 18H), 1.88 (t, *J* = 6.6 Hz, 3H).

**4-*n*-Tetradecyl-α-bromoacetophenone** (**16d**). Yield: 96%. $^1$H NMR (400 MHz, $CDCl_3$) *δ* 7.91 (d, *J* = 8.2 Hz, 2H, aromatic H), 7.29 (d, *J* = 8.2 Hz, 2H, aromatic H), 4.44 (s, 2H, $BrC\underline{H}_2$-), 2.67 (t, *J* = 7.6 Hz, 2H), 1.67-1.59 (m, 2H), 1.32-1.25 (m, 22H), 0.88 (t, *J* = 6.6 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) *δ* 191.08($BrCH_2\underline{C}O$-), 150.11, 131.79, 129.22, 129.05, 36.22, 32.06, 31.16, 31.09, 29.83, 29.81, 29.79, 29.78, 29.68, 29.58, 29.50, 29.40, 22.83, 14.26; HRMS (ESI), Calcd for $C_{22}H_{35}BrNaO$ $[M+Na]^+$, 417.1763; found, 417.1783.

**1-(2-Bromoethyl)-4-octyl benzene** (**17a).** Compound **17a** was prepared from **16a** by the procedure described in the general procedure. Yield: 96%. The product was used directly for the next step without purification.

**1-(2-Bromoethyl)-4-decyl benzene** (**17b).** Compound **17b** was prepared from **16b** by the procedure described in the general procedure. Yield: 97%. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.14-7.09 (m, 4H), 3.53 (t, *J* = 7.6 Hz, 2H), 3.12 (t, *J* = 7.7 Hz, 2H), 2.59-2.55 (m, 2H), 1.59-1.57 (m, 2H), 1.30-1.26 (m, 14H), 0.90-0.86 (m, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 141.75, 136.18, 128.75, 128.62, 39.26, 35.75, 33.19, 32.05, 31.63, 29.77, 29.74, 29.66, 29.49, 22.83, 14.26; HRMS (EI): Calcd for $C_{18}H_{29}Br$ $[M]^+$, 324.1447; found, 324.1444.

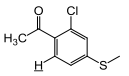
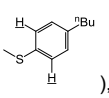
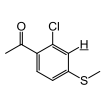
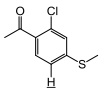
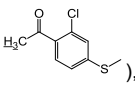
**1-(2-Bromoethyl)-4-dodecy benzene** (**17c**). Compound **17c** was prepared from **16c** by the procedure described in the general procedure. Yield: 96%. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.12 (t, *J* = 9.3 Hz, 4H), 3.55 (t, *J* = 7.6 Hz, 2H), 3.13 (t, *J* = 7.8 Hz, 2H), 2.57 (t, *J* = 7.7 Hz, 2H), 1.61-1.55 (m, 2H), 1.30-1.25 (m, 18H), 0.88 (t, *J* = 6.5 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 141.80, 136.22, 128.78, 128.65, 39.29, 35.76, 33.20, 32.08, 31.62, 29.82, 29.74, 29.66, 29.50, 22.84, 14.26; HRMS (EI): Calcd for $C_{20}H_{33}Br$ $[M]^+$, 352.1760; found, 352.1758.

**1-(2-Bromoethyl)-4-tetradecy benzene** (**17d**). Compound **17d** was prepared from **16d** by the procedure described in the general procedure. Yield: 97%. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.14-7.10 (m, 4H, aromatic H), 3.55 (t, *J* = 7.8 Hz, 2H, $BrC\underline{H}_2CH_2$-), 3.13 (t, *J* = 7.8 Hz, 2H, $BrCH_2C\underline{H}_2$-), 2.57 (t, *J* = 7.6 Hz, 2H), 1.63-1.55 (m, 2H), 1.30-1.25 (m, 22H), 0.88 (t, *J* = 6.8 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 141.80, 136.22, 128.78, 128.64, 39.29($BrCH_2\underline{C}H_2$-), 35.76 ($Br\underline{C}H_2CH_2$-), 33.20, 32.08, 31.62, 29.82, 29.74, 29.66, 29.51, 22.84, 14.26; HRMS (EI): Calcd for $C_{22}H_{37}Br$ $[M]^+$, 380.2073; found, 380.2071.

**4-(1-Heptyloxyl)-acetophenone** (**15e**). To a solution of 4-hydroxyl-acetophenone in anhydrous DMF (10 mL) was added 1-bromo-heptane (0.24 mL, 1.5 mmol). The mixture was stirred at 70 °C for 9 h until TLC indicated completion of the reaction. The mixture was allowed to warm to room temperature and ethyl acetate (40 mL) was added. The mixture was washed with water (2 × 10 mL) and brine (1× 10 mL). The combined organic layers were dried over $Na_2SO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography (petroleum ether/ethyl acetate, 20:1) to give the product as a brown oil. Yield: 344.8 mg (98%). $^1$H NMR (400 MHz, $CDCl_3$) δ 7.93-7.91 (m, 2H, aromatic H), 6.93-6.90 (m, 2H, aromatic H), 4.01 (t, *J* = 6.6 Hz, 2H, $C_6H_{13}C\underline{H}_2O$-), 2.55 (s, 3H, $CH_3CO$-), 1.84-1.77 (m, 2H), 1.49-1.42 (m, 2H), 1.40-1.31 (m, 6H), 0.90 (t, *J* = 6.8 Hz, 3H).

**1-(2-Bromoethyl)-4-(heptyloxy)benzene** (**17e)**. To a solution of compound **15e** (344.8 mg, 1.47 mmol) in EtOAc (7 mL) was added $CuBr_2$ (656.7 mg, 2.94 mmol) and the mixture was heated under reflux overnight. After TLC analysis showed the complete disappearance of the starting material, the mixture was cooled to room temperature and filtered. Saturated $Na_2S_2O_3$ aqueous solution was added into the filtrate, and the mixture was extracted with EtOAc. The organic layers were combined, dried ($Na_2SO_4$), filtered, and concentrated. The residue was used directly for the next step. The dimethylamine borane/titanium tetrachloride reduction provided compound **17e** as a light yellow oil (381.0 mg, 85%, over two steps). $^1$H NMR (400 MHz, $CDCl_3$) δ 7.10 (dd, *J* = 2.2 Hz, 8.6 Hz, 2H, aromatic H), 6.84 (dd, *J* = 3.0 Hz, 8.5 Hz, 2H, aromatic H), 3.93 (dt, *J* = 2.9 Hz, 6.5 Hz, 2H), 3.52 (dt, *J* = 1.8 Hz, 7.6 Hz, 2H), 3.09 (dt, *J* = 2.1 Hz, 7.7 Hz, 2H), 1.79-1.76 (m, 2H), 1.45-1.44 (m, 2H), 1.31 (br, 6H), 0.90-0.89 (m, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 158.23, 130.88, 129.70, 114.67, 68.09, 38.74, 33.50, 31.90, 29.40, 29.18, 26.13, 22.73, 14.21; HRMS (ESI): Calcd for $C_{15}H_{24}BrO$ $[M+H]^+$, 299.1005; found, 299.1010.

**4-(4-Butylphenoxy)-2-chloro-acetophenone** (**15f**). To a solution of *p-n*-butyl phenol (1.0 g, 5.80 mmol) in DMF (15 mL) was added $K_2CO_3$ (2.40 g, 17.38 mmol). The mixture was stirred at 50 °C for 30 min. Then 2-chloro-4-fluoro acetophenone (0.98 mL, 6.37 mmol) was added. The mixture was stirred at 115 °C under atmosphere of argon overnight. The mixture was cooled to room temperature and saturated $NH_4Cl$ was added, and extracted with EtOAc. The combined extracts were washed with saturated aqueous NaCl, dried over $Na_2SO_4$. The solvent was removed, and the product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate, 25:1) to give the product as a brown oil. Yield: 1.98 g (100%). $^1$H NMR (400 MHz, $CD_3OD$) δ 7.63 (d, *J* = 8.7 Hz, 1H), 7.21-7.19 (m, 2H), 6.97-6.95 (m, 3H), 6.87 (dd, *J* = 2.4 Hz, 8.6 Hz, 2H), 2.64-2.60 (m, 5H), 1.65-1.60 (m, 2H), 1.42-1.33 (m, 2H), 0.95 (t, *J* = 7.4 Hz, 3H).

**4-(4-Butylphenylthio)-2-chloro-acetophenone** (**15g**). Compound **15g** was prepared by the same procedure as **15f** from *p-n*-butyl thiophenol. Yield: 85%. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.48 (d, *J* = 8.2 Hz, 1H,  ), 7.42-7.39 (m, 2H,  ), 7.24-7.22 (m, 2H,  ), 7.11 (d, *J* = 1.8 Hz, 1H,  ), 7.01 (dd, *J* = 1.8 Hz, 8.2 Hz, 1H,  ), 2.65 (t, *J* = 7.7 Hz, 2H), 2.61 (s, 3H,  ), 1.66-1.59 (m, 2H), 1.42-1.33 (m, 3H), 0.94 (t, *J* = 7.4 Hz,

3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 199.09, 145.30, 144.74, 135.28, 134.60, 132.65, 130.43, 130.11, 128.49, 127.53, 125.29, 35.49, 33.48, 30.76, 22.46, 14.05; HRMS (ESI): Calcd for $C_{18}H_{20}OSCl$ $[M+H]^+$, 319.0918; found, 319.0923.

**4-(4-Butylphenoxy)-2-chloro-α-bromoacetophenone (16f)**. To a solution of compound **15f** (346.2 mg, 1.15 mmol) in MeCN ( 10 mL) was added NBS (214.2 mg, 1.20 mmol) and *p*-TsOH monohydrate (218.0 mg, 1.15 mmol). The mixture was heated at 50 °C overnight until TLC analysis showed the complete disappearance of the starting material. The reaction was quenched with saturated $NaHCO_3$ and extracted with $CH_2Cl_2$. The $CH_2Cl_2$ layers were combined, dried ($Na_2SO_4$), filtered, and concentrated. The residue was purified by column chromatography on silica gel (petroleum ether/EtOAc 25/1) to provide a light yellow solid (430.1 mg, 99%). $^1$H NMR (400 MHz, $CDCl_3$) δ 7.64 (d, *J* = 8.7 Hz, 1H), 7.22 (d, *J* = 8.4 Hz, 2H), 6.99-6.97 (m, 3H), 6.90 (dd, *J* = 2.4 Hz, 8.7 Hz, 1H), 4.53 (s, 2H), 2.63 (t, *J* = 7.6 Hz, 2H), 1.66-1.58 (m, 2H), 1.43-1.33 (m, 2H), 0.95 (t, *J* = 7.3 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 192.26, 162.08, 152.59, 140.28, 133.85, 132.81, 130.22, 129.42, 120.42, 119.10, 115.84, 35.15, 34.70, 33.79, 22.48, 14.07. HRMS (ESI): Calcd for $C_{18}H_{18}BrClNaO_2$ $[M+Na]^+$, 403.0071; found, 403.0084.

**1-(2-Bromoethyl)-4-(4-butylphenoxy)-2-chlorobenzene (17f)**. Compound **17f** was prepared from **16f** by the procedure described in the general procedure as a colorless oil. Yield: 72%. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.19-7.15 (m, 3H), 6.98 (d, *J* = 2.4 Hz, 1H), 6.93 (d, *J* = 8.4 Hz, 2H), 6.84 (dd, *J* = 2.5 Hz, 8.4 Hz, 1H), 3.56 (t, *J* = 7.5 Hz, 2H), 3.23 (t, *J* = 7.5 Hz, 2H), 2.60 (t, *J* = 7.6 Hz, 2H), 1.64-1.56 (m, 2H), 1.41-1.32 (m, 2H), 0.94 (t, *J* = 7.3 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 157.86, 154.10, 138.96, 134.65, 131.91, 130.60, 129.90, 119.56, 119.22, 116.75, 36.64, 35.09, 33.85, 31.30, 22.47, 14.08; HRMS (EI): Calcd for $C_{18}H_{20}OBrCl$ $[M]^+$, 366.0381; found, 366.0377.

**1-(2-Bromoethyl)-4-(4-butylphenylthio)-2-chloro-benzene** (**17g**). To a solution of compound **15g** (319.2 mg, 1.0 mmol) in EtOAc (7 mL) was added $CuBr_2$ (447.2 mg, 2.0 mmol) and the mixture was heated under reflux overnight. After TLC analysis showed the complete disappearance of the starting material, the mixture was cooled to room temperature and filtered. Saturated $Na_2S_2O_3$ aqueous solution was added into the filtrate, and the mixture was extracted with EtOAc for three times. The organic layers were combined, dried ($Na_2SO_4$), filtered, and concentrated. The residue was treated directly by the procedure described in the general procedure. Yield: 195.3 mg (51%, over two steps). $^1$H NMR (400 MHz, $CDCl_3$) δ 7.34 (d, *J* = 8.1 Hz, 2H), 7.20-7.12 (m, 4H), 7.06 (dd, *J* = 1.8 Hz, 8.0 Hz, 1H), 3.55 (t, *J* = 7.4 Hz, 2H), 3.23 (t, *J* = 7.5 Hz, 2H), 2.62 (t, *J* = 7.7 Hz, 2H), 1.64-1.56 (m, 2H), 1.41-1.31 (m, 2H), 0.93 (t, *J* = 7.3 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 143.64, 138.60, 134.60, 134.18, 133.23, 131.56, 129.84, 129.81, 129.56, 127.45, 36.84, 35.45, 33.57, 31.00, 22.49, 14.09; HRMS (ESI): Calcd for $C_{18}H_{21}BrClS$ $[M+H]^+$, 383.0230; found, 383.0212.

**1-(3-Chloro-4'-pentyl-(1,1'-biphenyl)-4-yl)ethan-1-one (15h)**. A mixture of 2-chloro-4-bromo-acetophenone (233.5 mg, 1.0 mmol), 4-pentylphenylboronic acid (230 mg, 1.19 mmol), tetrakis(triphenylphosphine)palladium(0) (12.0 mg, 0.010 mmol), and $NaHCO_3$ (504 mg, 5.99 mmol) in 1,2-dimethoxyethane (6.0 mL) and water (2.0 mL) was heated at 65 °C for 4 h. Water was added to the reaction mixture, and the resulting mixture was extracted with EtOAc. The organic layer was washed with brine, dried over $Na_2SO_4$, and concentrated in vacuo. Purification of the residue by column chromatography on silica gel (toluene/MeCN 300:1) gave the title compound (450 mg, 80%) as a light yellow solid. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.68-7.63 (m, 2H), 7.54-7.49 (m, 3H), 7.28 (d, *J* = 8.1 Hz, 2H), 2.69-2.63 (m, 5H), 1.68-1.61 (m, 2H), 1.36-1.32 (m, 2H), 0.90 (t, *J* = 6.6 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 199.85, 145.46, 143.86, 136.93, 135.97, 132.30, 130.44, 129.26, 129.12, 127.12, 125.37, 35.73, 31.63, 31.21, 30.88, 22.67, 14.15; HRMS (ESI): Calcd for $C_{19}H_{22}ClO$ $[M+H]^+$, 301.1354; found, 301.1355.

**4-(2-Bromoethyl)-3-chloro-4'-pentyl-1,1'-biphenyl (17h)**. Compound **17h** was synthesized starting from **15h** using a similar procedure to that described in the preparation of **17f**, yielding **17h** as a light yellow oil (47% yield over two steps). $^1$H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, *J* = 1.8 Hz, 1H), 7.47 (d, *J* = 8.2 Hz, 2H), 7.43 (dd, *J* = 1.8 Hz, 7.9 Hz, 1H), 7.30 (d, *J* = 7.9 Hz, 2H), 7.25-7.24 (m, 2H), 3.62 (t, *J* = 7.4 Hz, 2H), 3.32 (t, *J* = 7.6 Hz, 2H), 2.64 (t, *J* = 7.6 Hz, 2H), 1.68-1.61 (m, 2H), 1.36-1.33 (m, 4H), 0.90 (t, *J* = 6.8 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 143.00, 141.98, 136.85, 134.94, 134.48, 131.49, 129.13, 128.18, 126.96, 125.55, 37.05, 35.73, 31.68, 31.24, 31.08, 22.69, 14.15; HRMS (EI): Calcd for $C_{19}H_{22}BrCl$ $[M]^+$, 364.0588; found, 364.0586.

**1-(4'-Bromo-3-chloro-(1,1'-biphenyl)-4-yl)ethan-1-one (19)**. A mixture of 2-chloro-4-bromo-acetophenone (233.5 mg, 1.0 mmol), bis(neopentyl glycolato)diboron (248.5 mg, 1.1 mmol), potassium acetate (294.4 mg, 3.0 mmol), and dichlorobis(tricyclohexylphosphine)palladium(II) (36.9 mg, 0.05 mmol) in 1,4-dioxane (4 mL) was heated at 100 °C. After 6 h, the mixture was allowed to cool to room temperature and poured into water. The mixture was extracted with EtOAc and washed with brine. The organic layer was dried over $Na_2SO_4$ and concentrated in vacuo. The residue was used directly for the next step.

The product obtained from above, 1-bromo-4-iodobenzene (278.7 mg, 0.99 mmol) and $NaHCO_3$ (470.5 mg, 5.6 mmol) in 1,2-dimethoxyethane (6 mL) and water (2 mL) was added tetrakis-(triphenylphosphine)palladium(0) (22.0 mg, 0.02 mmol). After stirring at 100 °C for 8 h, 1-bromo-4-iodobenzene (133.0 mg, 0.47 mmol) and tetrakis(triphenylphosphine)palladium(0) (11.6 mg, 0.01 mmol) was added to the mixture. The mixture was stirred at 100 °C for another 8 h and extracted with EtOAc. The organic layer was washed with brine, dried over $Na_2SO_4$, and concentrated in vacuo. Purification of the residue by column chromatography on silica gel (petroleum ether /EtOAc 25:1) gave the title compound as a brown solid. Yield: 164.1 mg, 53%. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, *J* = 8.0 Hz, 1H), 7.60-7.57 (m, 3H), 7.49 (dd, *J* = 1.7 Hz, 8.0 Hz, 1H), 7.46-7.42 (m, 2H), 2.68 (s, 3H).

**1-(3-Chloro-4'-(*p*-tolylthio)-(1,1'-biphenyl)-4-yl)ethan-1-one** (**15i**). A mixture of **19** (327.3 mg, 1.06 mmol), *p*-toluene thiophenol (148.4 mg, 1.20 mmol), tris(dibenzylideneacetone)dipalladium(0)-chloroform adduct (27.4 mg, 0.03 mmol), 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (Xantphos, 30.6 mg, 0.05 mmol), and *N,N*-diisopropylethylamine (0.36 mL, 2.11 mmol) in 1,4-dioxane (10.0mL) was refluxed overnight. After being poured into water, the mixture was extracted with EtOAc. The organic layer was washed with brine, dried over $Na_2SO_4$, and concentrated in vacuo. Purification of the residue by column chromatography on silica gel (petroleum ether/dichloromethane 1:2) gave the title compound as a pale-yellow solid. Yield: 325.4 mg, 87%. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.67-7.64 (m, 1H), 7.60-7.57 (m, 1H), 7.49-7.44 (m, 3H), 7.36 (d, *J* = 8.1 Hz, 2H), 7.28 (d, *J* = 8.4 Hz, 2H), 7.18 (d, *J* = 8.0 Hz, 2H), 2.67 (s, 3H), 2.37 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 199.69, 144.58, 139.05, 138.44, 137.19, 136.24, 133.25, 132.34, 132.32, 130.47, 130.39, 129.39, 128.97, 127.70, 125.23, 30.83, 21.31; HRMS (ESI): Calcd for $C_{21}H_{17}OSCl$ $[M+H]^+$, 353.0762; found, 353.0775.

**(4'-(2-Bromoethyl)-3'-chloro-(1,1'-biphenyl)-4-yl)(*p*-tolyl)sulfane (17i)**. Compound **17i** was synthesized starting from **15i** using a similar procedure to that described in the preparation of **17e**, yielding **17i** as a light yellow oil. Yield: 118.0 g, 57% over two steps. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.56-7.55 (m, 1H), 7.46-7.43 (m, 2H), 7.40 (dd, *J* = 1.7 Hz, 8.0 Hz, 1H), 7.35 (d, *J* = 8.1 Hz, 2H), 7.31-7.28 (m, 3H), 7.17 (d, *J* = 7.9 Hz, 2H), 3.61 (t, *J* = 7.4 Hz, 2H), 3.31 (t, *J* = 7.5 Hz, 2H), 2.36 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 141.14, 138.16, 137.64, 137.43, 135.35, 134.59, 133.15, 132.88, 131.62, 130.34, 129.88, 128.08, 127.63, 125.44,

36.98, 31.03, 21.31; HRMS (ESI): Calcd for $C_{21}H_{19}BrClS$ $[M+H]^+$, 417.0074; found, 417.0078.

**2-Bromo-*N*-(3-octylphenyl)acetamide (17j)**. 3-Bromo nitrobenzene (2.02 g, 10 mmol) and $[Pd(PPh_3)_2Cl_2]$ (140 mg, 0.2 mmol) were dissolved in dry $Et_3N$ (10 mL), and the solution was argon-degassed for 10 min. Then CuI (76.2 mg, 0.4 mmol) was added, and the solution was argon-degassed for another 10 min after which 1-octyne (1.7 mL, 11.8 mmol) was added via a syringe. The reaction was stirred under an atmosphere of argon overnight at 60 °C and was then quenched with water, extracted with heptane, washed with brine, dried ($Na_2SO_4$), evaporated to dryness and the crude product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate, 50/1). The product 1-nitro-3-octynylbenzene (**15j**) was obtained as brown oil (2.2 g, 95%).

Compound **15j** (220.5 mg, 0.95 mmol) was dissolved in MeOH (5 mL) and Pd/C (10%, 100 mg) was added, and the mixture was hydrogenated at 0.4 MPa of $H_2$ (g) overnight. The Pd/C was removed by filtration on celite and the filtrate was evaporated to drynesss, affording 3-octylaniline (**16j**). The residue was used directly for the next step.

The crude product above was dissolved in 5 mL of $CH_2Cl_2$ and the mixture was cooled to 0 °C. Bromoacetyl bromide (42.4 µL, 0.53 mmol) and $Et_3N$ (76.1 µL, 0.55 mmol) were added dropwise at 0 °C, and the reaction mixture was stirred overnight while being allowed to warm to room temperature. The mixture was concentrated in vacuo and the residue was purified by column chromatography on silica gel (petroleum ether/EtOAc 5/1) to provide **17j** as a white solid. Yield: 172.0 mg, 58%. $^1$H NMR (400 MHz, $CDCl_3$) δ 8.14 (s, 1H), 7.36-7.34 (m, 2H), 7.27-7.23 (m, 1H), 6.99 (d, *J* = 7.5 Hz, 1H), 4.01 (s, 2H), 2.59 (t, *J* = 7.6 Hz, 2H), 1.61-1.58 (m, 2H), 1.29-1.26 (m, 10H), 0.89-0.86 (m, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 163.43, 144.36, 136.95, 129.05, 125.50, 120.13, 117.49, 36.06, 32.01, 31.52, 29.69, 29.59, 29.45, 29.37, 22.79, 14.24; HRMS (ESI): Calcd for $C_{16}H_{25}NOBr$ $[M+H]^+$, 326.1115; found, 326.1118.

**2-Bromo-*N*-(3-hexylphenyl)acetamide (17k)**. Compound **17k** was synthesized starting from 3-bromo nitrobenzene and 1-hexyne using a similar procedure to that described in the preparation of **17j**, yielding **17k** as a white solid. Yield: 107.4 mg, 36%. $^1$H NMR (400 MHz, $CDCl_3$) δ 8.28 (s, 1H), 7.35 (s, 2H), 7.24 (t, *J* = 7.6 Hz, 1H), 6.98 (d, *J* = 7.4 Hz, 1H), 3.99 (s, 2H), 2.58 (t, *J* = 7.8 Hz, 2H), 1.61-1.55 (m, 2H), 1.29 (br, 6H), 0.88-0.86 (M, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 163.71, 144.29, 136.98, 128.99, 125.45, 120.16, 117.53, 36.01, 31.79, 31.44, 29.65, 29.07, 22.69, 14.19; HRMS (ESI): Calcd for $C_{14}H_{21}NOBr$ $[M+H]^+$, 298.0802; found, 298.0812.

**4-(4-Butylphenoxy)-2-chloro-1-nitrobenzene (15l)**. To a solution of 2-fluoro-4-chloronitrobenzene (263.3 mg, 1.5 mmol) in DMF (10 mL) was added 4-butylphenol (0.25 mL, 1.65 mmol) and $K_2CO_3$ (310.9 mg, 3.0 mmol). The mixture was stirred at 70 °C overnight. After TLC analysis showed the complete disappearance of the starting material, the mixture was cooled to room temperature, neutralized with saturated $NH_4Cl$ aqueous solution, extracted with EtOAc. The EtOAc layers were combined, dried ($Na_2SO_4$), filtered, and concentrated. The residue was purified by column chromatography on silica gel (petroleum ether/EtOAc 35:1) to provide **15l** (458.6 mg, 100%) as a light yellow solid. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, *J* = 9.1 Hz, 1H), 7.24 (d, *J* = 8.4 Hz, 2H), 7.03 (d, *J* = 2.6 Hz, 1H), 6.99-6.97 (m, 2H), 6.90 (dd, *J* = 2.6 Hz, 9.1 Hz, 1H), 2.64 (t, *J* = 7.7 Hz, 2H), 1.66-1.59 (m, 2H), 1.43-1.34 (m, 2H), 0.95 (t, *J* = 7.3 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 162.18, 152.14, 141.90, 140.78, 130.38, 129.73, 128.07, 120.50, 119.62, 115.54, 35.14, 33.75, 22.46, 14.07; HRMS (ESI): Calcd for $C_{16}H_{17}ClNO_3$ $[M+H]^+$, 306.0891; found, 306.0897.

**2-Bromo-*N*-(4-(4-butylphenoxy)phenyl)acetamide (17l)**. To a solution of compound **15l** (153.0 mg, 0.5 mmol) in MeOH (5 mL) was added 10% Pd/C (53.2 mg, 0.05 mmol). The mixture was stirred under 0.4 MPa of $H_2$ pressure at room temperature overnight. After TLC analysis showed the complete disappearance of the starting material, the mixture was filtered and the filtrate was concentrated in vacuo, the residue was used directly for the next step. The crude product was dissolved in 5 mL of $CH_2Cl_2$, bromoacetyl bromide (42.4 µL, 0.53 mmol) and $Et_3N$ (76.1 µL, 0.55 mmol) were added dropwise at 0 °C. The mixture was warmed to room temperature and stirred overnight. The mixture was concentrated in vacuo and purified by column chromatography on silica gel (petroleum ether/EtOAc 5:1) to provide **17l** (137.7 mg, 76%) as a light yellow solid. $^1$H NMR (400 MHz, $CDCl_3$) δ 8.20 (br, 1H), 7.47-7.43 (m, 2H), 7.14-7.12 (m, 2H), 6.99-6.95 (m, 2H), 6.92-6.88 (m, 2H), 4.01 (s, 2H), 2.58 (t, *J* = 7.6 Hz, 2H), 1.62-1.55 (m, 2H), 1.40-1.31 (m, 2H), 0.93 (t, *J* = 7.3 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 163.60, 155.02, 154.99, 138.21, 132.02, 129.73, 122.06, 119.15, 118.85, 35.01, 33.87, 29.56, 22.44, 14.07; HRMS (ESI): Calcd for $C_{18}H_{21}NO_2Br$ $[M+H]^+$, 362.0751; found, 362.0756.

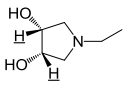
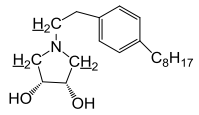
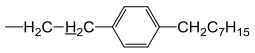
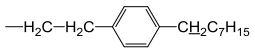
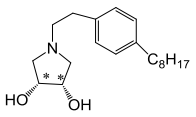
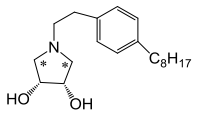
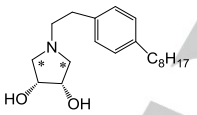
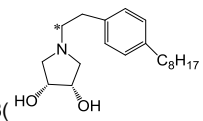
**2-Bromo-*N*-(4-(4-butylphenoxy)-2-chloro-phenyl)acetamide (17m)**. To a solution of compound **15l** (76.4 mg, 0.25 mmol) in MeOH ( 2.5 mL) was added zinc powder (163.5 mg, 2.5 mmol) and $NH_4Cl$ solid (133.7 mg, 2.5 mmol). The mixture was stirred at 45 °C for 8 h. After TLC analysis showed the complete disappearance of the starting material, the mixture was diluted with EtOAc, filtered, and the filtrate was concentrated in vacuo. The residue was treated directly by the same procedure as for the preparation of **17l** to provide compound **17m** (89.3 mg, 90%) as white solid. $^1$H NMR (400 MHz, $CDCl_3$) δ 8.66 (s, 1H), 8.21 (d, *J* = 9.0 Hz, 1H), 7.16 (d, *J* = 8.5 Hz, 2H), 7.03 (d, *J* = 2.7 Hz, 1H), 6.94-6.91 (m, 3H), 4.07 (s, 2H), 2.60 (t, *J* = 7.6 Hz, 2H), 1.63-1.56 (m, 2H), 1.41-1.32 (m, 2H), 0.94 (t, *J* = 7.3 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 163.39, 155.04, 154.26, 138.91, 129.91, 129.04, 124.73, 122.69, 119.26, 118.96, 117.57, 35.06, 33.84, 29.67, 22.45, 14.08; HRMS (ESI): Calcd for $C_{18}H_{20}BrClNO_2$ $[M+H]^+$, 396.0360; found, 396.0349.

**1-(Heptyloxy)-4-nitrobenzene (15n)**. To a solution of 4-nitro-phenol (556.4 mg, 5.0 mmol) and 1-bromoheptane (0.79 mL, 5.0 mmol) in DMF (10 mL) was added $K_2CO_3$. The mixture was stirred at 70 °C for 6 h until TLC showed the completion of the reaction. The mixture was cooled to room temperature and neutralized with saturated $NH_4Cl$ aqueous solution and extracted with EtOAc for three times. The organic layers were combined and washed with brine, dried ($Na_2SO_4$), filtered, and concentrated. The residue was purified by column chromatography on silica gel (petroleum ether/EtOAc 20:1) to afford **15n** as a yellow oil. Yied: 949.2 mg, 80%. $^1$H NMR (400 MHz, $CDCl_3$) δ 8.22-8.18 (m, 2H), 6.96-6.92 (m, 2H), 4.05 (t, *J* = 6.5 Hz, 2H), 1.86-1.79 (m, 2H), 1.50-1.43 (m, 2H), 1.40-1.29 (m, 6H), 0.90 (t, *J* = 6.8 Hz, 3H).

**2-Bromo-*N*-(4-(heptyloxy)phenyl)acetamide (17n)**. Compound **17n** was synthesized starting from **15n** (936.6 mg, 3.95 mmol) using a similar procedure to that described in the preparation of **17m**, yielding **17n** as a white solid. Yield: 842.8 mg, 65% over two steps. $^1$H NMR (400 MHz, $CDCl_3$) δ 8.04 (s, 1H), 7.42-7.40 (m, 2H), 6.89-6.87 (m, 2H), 4.02 (s, 2H), 3.94 (t, *J* = 6.6 Hz, 2H), 1.80-1.73 (m, 2H), 1.48-1.41 (m, 2H), 1.39-1.26 (m, 6H), 0.89 (t, *J* = 6.7 Hz, 3H).

**(3R,4S)-3,4-Di-*O*-isopropylidene-1-(4-octylphenylethyl)pyrrolidine (18a).** To a solution of compound **17a** (117.1 mg, 0.39 mmol) and compound **11** (91.9 mg, 0.39 mmol) in anhydrous acetonitrile (10 mL) was added potassium carbonate (54.4 mg, 0.39 mmol). The mixture was stirred at 50 °C overnight until TLC analysis showed the complete disappearance of the starting material. The mixture was cooled to room temperature, filtered and concentrated in vacuo. The residue was purified by column chromatography on silica gel (petroleum ether/acetone 15:1) to provide compound **18a** (53.8 mg, 38%) as a light yellow oil. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.12-7.06 (m, 4H), 4.66-4.63 (m, 2H), 3.14 (d, *J* = 11.2 Hz, 2H), 2.79-2.75 (m, 2H), 2.65-2.61 (m, 2H), 2.55 (t, *J* = 7.6 Hz, 2H), 2.15-2.12 (m, 2H), 1.59-1.54 (m, 2H), 1.52 (s, 3H), 1.32-1.26 (m, 13H), 0.87 (t, *J* = 6.5 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 140.69, 137.54, 128.65, 128.42, 111.16, 79.49, 60.18, 57.72, 35.68, 34.84, 32.00,

31.69, 29.60, 29.48, 29.37, 26.38, 24.88, 22.78, 14.22; HRMS (ESI): Calcd for $C_{23}H_{38}NO_2$ $[M+H]^+$, 360.2898; found, 360.2897.

**(3R,4S)-1-(4-Octylphenylethyl)pyrrolidine-3,4-diol (10a)**. Compound **10a** was prepared from **18a** by the procedure described in the general procedure as a light yellow solid (86% yield). $^1$H NMR (400 MHz, MeOD) δ 7.17-7.10 (m, 4H, aromatic H ), 4.31 (s, 2H,  ), 3.11-3.03 (m, 6H,  ), 2.90-2.86 (m, 2H,  ), 2.56 (t, *J* = 7.5 Hz, 2H,  ), 1.60-1.56 (m, 2H), 1.31-1.28 (m, 10H), 0.89 (t, *J* = 6.7 Hz, 3H); $^{13}$C NMR (100 MHz, MeOD) δ 142.46, 136.47, 129.75, 129.61, 71.36(  ), 60.41(  ), 59.39(  ), 36.48(  ), 33.94, 33.00, 32.73, 30.55, 30.38, 30.29, 23.69, 14.42; HRMS (ESI): Calcd for $C_{20}H_{34}NO_2$ $[M+H]^+$, 320.2585; found, 320.2589.

**(3R,4S)-3,4-Di-*O*-isopropylidene-1-(4-decylphenylethyl)pyrrolidine (18b).** Compound **18b** was prepared from **17b** as described in the preparation of compound 1**8a**. Yield: 35% as a light yellow oil after column chromatography (petroleum ether/acetone 15:1). $^1$H NMR (400 MHz, $CDCl_3$) δ 7.12-7.06 (m, 4H), 4.65 (m, 2H), 3.15 (d, *J* = 10.8 Hz, 2H), 2.78-2.74 (m, 2H), 2.65-2.61 (m, 2H), 2.55 (t, *J* = 8.0 Hz, 2H), 2.14-2.12 (m, 2H), 1.58-1.52 (m, 5H), 1.31-1.26 (m, 17H), 0.88-0.87 (m, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 140.54, 137.40, 128.55, 128.32, 111.07, 79.39, 60.06, 57.60, 35.60, 34.72, 31.94, 31.61, 29.67, 29.64, 29.56, 29.38, 26.29, 24.81, 22.71, 14.16; HRMS (ESI): Calcd for $C_{25}H_{42}NO_2$ $[M+H]^+$, 388.3211; found, 388.3205.

**(3R,4S)-1-(4-Decylphenylethyl)pyrrolidine-3,4-diol (10b)**. Compound **10b** was prepared from **18b** as described in the preparation of compound 1**0a**. Yield: 77% as a light yellow solid after column chromatography. $^1$H NMR (400 MHz, $CD_3OD$) δ 7.20 (d, *J* = 7.7 Hz, 2H), 7.14 (d, *J* = 7.9 Hz, 2H), 4.37 (s, 2H), 3.53-3.49 (m, 2H), 3.42-3.35 (m, 4H), 3.00 (t, *J* = 8.4 Hz, 2H), 2.57 (t, *J* = 7.5 Hz, 2H), 1.60-1.56 (m, 2H), 1.30-1.28 (m, 14H), 0.91-0.87 (m, 3H); $^{13}$C NMR (100 MHz, MeOD) δ 142.94, 134.85, 129.91, 129.72, 71.04, 59.21, 59.08, 36.46, 33.00, 32.64, 32.47, 30.67, 30.55, 30.39, 30.26, 23.68, 14.43; HRMS (ESI): Calcd for $C_{22}H_{38}NO_2$ $[M+H]^+$, 348.2898; found, 348.2906.

**(3R,4S)-3,4-Di-*O*-isopropylidene-1-(4-dodecylphenylethyl)pyrrolidine (18c)**. Compound **18c** was prepared from **17c** as described in the preparation of compound 1**8a**. Yield: 43% as a light yellow oil after column chromatography (petroleum ether/acetone 15:1). $^1$H NMR (400 MHz, $CDCl_3$) δ 7.11 (d, *J* = 8.0 Hz, 2H), 7.06 (d, *J* = 8.0 Hz, 2H), 4.65-4.63 (m, 2H), 3.15 (d, *J* = 11.1 Hz, 2H), 2.78-2.74 (m, 2H), 2.65-2.61 (m, 2H), 2.54 (t, *J* = 7.7 Hz, 2H), 2.15-2.13 (m, 2H), 1.57-1.56 (m, 2H), 1.51 (s, 3H), 1.31-1.25 (m, 21H), 0.88 (t, *J* = 6.2 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 140.60, 137.41, 128.59, 128.37, 111.11, 79.41, 60.06, 57.64, 35.63, 34.72, 31.99, 31.64, 29.75, 29.71, 29.67, 29.60, 29.43, 26.29, 24.81, 22.76, 14.20; HRMS (ESI): Calcd for $C_{27}H_{46}NO_2$ $[M+H]^+$, 416.3524; found, 416.3522.

**(3R,4S)-1-(4-Dodecylphenylethyl)pyrrolidine-3,4-diol (10c)**. Compound **10c** was prepared from **18c** as described in the preparation of compound 1**0a**. Yield: 97% as a light yellow solid after column chromatography. $^1$H NMR (400 MHz, $CD_3OD$) δ 7.15 (d, *J* = 7.9 Hz, 2H), 7.10 (d, *J* = 7.8 Hz, 2H), 4.31-4.27 (m, 2H), 3.44-3.40 (m, 2H), 3.27-3.24 (m, 4H), 2.93 (t, *J* = 8.6 Hz, 2H), 2.53 (t, *J* = 7.5 Hz, 2H), 1.58-1.51 (m, 2H), 1.27-1.24 (m, 18H), 0.86 (t, *J* = 6.6 Hz, 3H); $^{13}$C NMR (100 MHz, $CD_3OD$) δ 142.88, 135.17, 129.90, 129.69, 71.10, 59.32, 59.17, 36.48, 33.04, 32.72, 32.67, 30.74, 30.71, 30.56, 30.43, 30.28, 23.70, 14.44; HRMS (ESI): Calcd for $C_{24}H_{42}NO_2$ $[M+H]^+$, 376.3211; found, 376.3216.

**(3R,4S)-3,4-Di-*O*-isopropylidene-1-(4-tetradecylphenylethyl)pyrrolidine (18d)**. Compound **18d** was prepared from **17d** as described in the preparation of compound 1**8a**. Yield: 44% as a yellow solid after column chromatography (petroleum ether/ acetone 15:1). $^1$H NMR (400 MHz, $CDCl_3$) δ 7.11-7.05 (m, 4H), 4.65-4.61 (m, 2H), 3.15 (d, *J* = 11.1 Hz, 2H), 2.78-2.74 (m, 2H), 2.65-2.61 (m, 2H), 2.54 (t, *J* = 7.7 Hz, 2H), 2.13 (d, *J* = 9.6 Hz, 2H), 1.61-1.51 (m, 5H), 1.31-1.25 (m, 25H), 0.88 (t, *J* = 6.3 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 140.56, 137.37, 128.57, 128.34, 111.09, 79.38, 60.03, 57.62, 35.62, 34.69, 31.99, 31.63, 29.74, 29.66, 29.59, 29.42, 26.26, 24.79, 22.74, 14.18; HRMS (ESI): Calcd for $C_{29}H_{50}NO_2$ $[M+H]^+$, 444.3837; found, 444.3838.

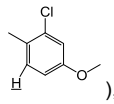
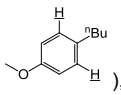
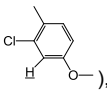
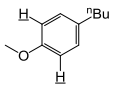
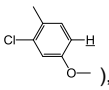
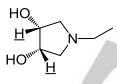
**(3R,4S)-1-(4-Tetradecylphenylethyl)pyrrolidine-3,4-diol (10d)**. Compound **10d** was prepared from **18d** as described in the preparation of compound 1**0a**. Yield: 89% as a light yellow solid after column chromatography. $^1$H NMR (400 MHz, $CD_3OD$) δ 7.18 (d, *J* = 7.8 Hz, 2H), 7.12 (d, *J* = 7.7 Hz, 2H), 4.33 (s, 2H), 3.48 (dd, *J* = 4.7 Hz, 11.4 Hz, 2H), 3.35–3.27 (m, 4H), 2.99–2.95 (m, 2H), 2.56 (t, *J* = 7.6 Hz, 2H), 1.58 (br, 2H), 1.28 (br, 22H), 0.89 (t, *J* = 6.5 Hz, 3H); $^{13}$C NMR (100 MHz, $CD_3OD$) δ 142.79, 135.19, 129.86, 129.70, 71.09, 59.31, 59.04, 36.51, 33.06, 32.67, 30.76, 30.60, 30.46, 30.33, 23.72, 14.50; HRMS (ESI): Calcd for $C_{24}H_{46}NO_2$ $[M+H]^+$, 404.3524; found, 404.3516.

**(3R,4S)-3,4-Di-*O*-isopropylidene-1-(4-heptyloxylphenylethyl)pyrrolidine (18e)**. Compound **18e** was prepared from **17e** as described in the preparation of compound 1**8a**. Yield: 93% as a yellow solid after column chromatography (petroleum ether/ acetone 7:1). $^1$H NMR (400 MHz, $CDCl_3$) δ 7.10 (d, *J* = 8.0 Hz, 2H), 6.80 (d, *J* = 8.1 Hz, 2H), 4.63 (s, 2H), 3.91 (t, *J* = 6.3 Hz, 2H), 3.13 (d, *J* = 10.8 Hz, 2H), 2.75-2.71 (m, 2H), 2.62-2.58 (m, 2H), 2.12 (d, *J* = 10.0 Hz, 2H), 1.79-1.72 (m, 2H), 1.52 (s, 3H), 1.47-1.40 (m, 2H), 1.36-1.25 (m, 9H), 0.90-0.87 (m, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 157.55, 132.29, 129.62, 114.41, 111.11, 79.46, 68.03, 60.15, 57.83, 34.33, 31.87, 29.40, 29.15, 26.38, 26.10, 24.87, 22.68, 14.17; HRMS (ESI): Calcd for $C_{22}H_{36}NO_3$ $[M+H]^+$, 362.2690; found, 362.2692.

**(3R,4S)-1-(4-Heptyloxylphenylethyl)pyrrolidine-3,4-diol (10e)**. Compound **10e** was prepared from **18e** as described in the preparation of compound 1**0a**. Yield: 60% as a white solid after column chromatography. $^1$H NMR (400 MHz, $CD_3OD$) δ 7.20 (d, *J* = 8.5 Hz, 2H), 6.88 (d, *J* = 8.6 Hz, 2H), 4.36 (s, 2H), 3.94 (t, *J* = 6.4 Hz, 2H), 3.47-3.43 (m, 4H), 2.99 (t, *J* = 8.5 Hz, 2H), 1.79-1.72 (m, 2H), 1.49-1.42 (m, 2H), 1.40-1.33 (m, 6H), 0.91 (t, *J* = 6.7 Hz, 3H); $^{13}$C NMR (100 MHz, $CD_3OD$) δ 159.82, 130.85, 129.14, 115.96, 71.03, 69.02, 59.00, 32.95, 31.88,

30.38, 30.17, 27.11, 23.64, 14.40; HRMS (ESI): Calcd for $C_{19}H_{32}NO_3$ $[M+H]^+$, 322.2377; found, 322.2383.

**(3R,4S)-3,4-Di-*O*-isopropylidene-1-(4-(4-butylphenoxy)-2-chlorophenylethyl)pyrrolidine (18f)**. Compound **18f** was prepared from **17f** as described in the preparation of compound 1**8a**. Yield: 38% as a yellow oil after column chromatography (petroleum ether/ acetone 20:1). $^1$H NMR (400 MHz, $CDCl_3$) δ 7.20 (d, *J* = 8.4 Hz, 1H), 7.16-7.12 (m, 2H), 6.96 (d, *J* = 2.5 Hz, 1H), 6.93-6.89 (m, 2H), 6.81 (dd, *J* = 2.5 Hz, 8.4 Hz, 1H), 4.68-4.65 (m, 2H), 3.18 (d, *J* = 11.4 Hz, 2H), 2.91-2.87 (m, 2H), 2.68-2.64 (m, 2H), 2.59 (t, *J* = 7.6 Hz, 2H), 2.23-2.20 (m, 2H), 1.63-1.56 (m, 2H), 1.51 (s, 3H), 1.41-1.33 (m, 2H), 1.32 (s, 3H), 0.93 (t, *J* = 7.4 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 156.92, 154.47, 138.62, 134.46, 132.15, 131.59, 129.81, 119.26, 119.17, 116.97, 111.29, 79.49, 59.98, 55.51, 35.07, 33.87, 31.87, 26.34, 24.88, 22.47, 14.09; HRMS (ESI): Calcd for $C_{25}H_{33}NO_3Cl$ $[M+H]^+$, 430.2144; found, 430.2142.

**(3R,4S)-1-(4-(4-Butylphenoxy)-2-chlorophenylethyl)pyrrolidine-3,4-diol (10f)**. Compound **10f** was prepared from **18f** as described in the preparation of compound 1**0a**. Yield: 90% as a yellow viscous oil after column chromatography. $^1$H NMR (400 MHz, $CD_3OD$) δ 7.25, (d, *J* = 8.5 Hz, 1H,  ), 7.14 (d, *J* = 8.4 Hz, 2H,  ), 6.90 (d, *J* = 2.4 Hz, 1H,  ), 6.86 (d, *J* = 8.4 Hz, 2H,  ), 6.80 (dd, *J* = 2.4 Hz, 8.4 Hz, 1H,  ), 4.30 (s, 2H,  ), 2.95-2.91 (m, 6H), 2.80-2.76 (m, 2H), 2.56 (t, *J* = 7.6 Hz, 2H), 1.60-1.52 (m, 2H), 1.38-1.29 (m, 2H), 0.91 (t, *J* = 7.3 Hz, 3H); $^{13}$C NMR (100 MHz, $CD_3OD$) δ 158.72, 155.42, 139.94, 135.35, 132.82, 131.96, 130.84, 120.34, 119.82, 117.93, 71.50, 61.10, 57.45, 35.85, 34.92, 32.17, 23.28, 14.31; HRMS (ESI): Calcd for $C_{22}H_{29}NO_3Cl$ $[M+H]^+$, 390.1831; found, 390.1840.

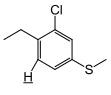
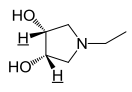
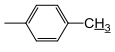
**(3R,4S)-3,4-Di-*O*-isopropylidene-1-(4-((4-butylphenyl)thio)-2-chlorophenylethyl)pyrrolidine (18g)**. Compound **18g** was prepared from **17g** as described in the preparation of compound 1**8a**. Yield: 77% as a yellow oil after column chromatography (petroleum ether/ acetone 10:1). $^1$H NMR (400 MHz, $CDCl_3$) δ 7.31-7.29 (m, 2H), 7.22 (d, *J* = 1.8 Hz, 1H), 7.18-7.13 (m, 3H), 7.05 (dd, *J* = 1.9 Hz, 8.0 Hz, 1H), 4.67-4.63 (m, 2H), 3.15 (d, *J* = 11.3 Hz, 2H), 2.88 (t, *J* = 7.2 Hz, 2H), 2.65-2.58 (m, 4H), 2.20-2.17 (m, 2H), 1.63-1.55 (m, 2H), 1.49 (s, 3H), 1.40-1.33 (m, 2H), 1.31 (s, 3H), 0.93 (t, *J* = 7.3 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 143.15, 136.70, 136.17, 134.56, 132.56, 131.35, 130.77, 130.10, 129.66, 128.15, 111.27, 79.50, 59.99, 55.18, 35.40, 33.56, 32.18, 26.38, 24.95, 22.46, 14.05; HRMS (ESI): Calcd for $C_{25}H_{33}NO_2SCl$ $[M+H]^+$, 446.1916; found, 446.1917.

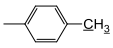
**(3R,4S)-1-(4-((4-Butylphenyl)thio)-2-chlorophenethyl)pyrrolidine-3,4-diol (10g)**. Compound **10g** was prepared from **18g** as described in the preparation of compound 1**0a**. Yield: 85% as a white solid after column chromatography. $^1$H NMR (400 MHz, $CD_3OD$) δ 7.31-7.29 (m, 2H), 7.24 (d, *J* = 8.1 Hz, 1H), 7.19-7.17 (m, 2H), 7.14 (d, *J* = 1.9 Hz, 1H), 7.06 (dd, *J* = 1.9 Hz, 8.0 Hz, 1H), 4.28-4.24 (m, 2H), 3.28-3.24 (m, 2H), 3.06-2.97 (m, 6H), 2.60 (t, *J* = 7.6 Hz, 2H), 1.62-1.54 (m, 2H), 1.39-1.30 (m, 2H), 0.92 (t, *J* = 7.3 Hz, 3H); $^{13}$C NMR (100 MHz, $CD_3OD$) δ 144.90, 139.84, 135.49, 134.59, 134.28, 132.57, 130.81, 130.21, 128.79, 71.24, 59.78, 57.26, 36.21, 34.67, 31.42, 23.33, 14.30; HRMS (ESI): Calcd for $C_{22}H_{29}NO_2SCl$ $[M+H]^+$, 406.1603; found, 406.1605.

**(3R,4S)-3,4-Di-*O*-isopropylidene-(1-(2-(3-chloro-4'-pentyl-(1,1'-biphenyl)-4-yl)ethyl)pyrrolidine (18h)**. Compound **18h** was prepared from **17h** as described in the preparation of compound 1**8a**. Yield: 21% as a yellow oil after column chromatography (petroleum ether/ acetone 9:1). $^1$H NMR (400 MHz, $CDCl_3$) δ 7.55 (s, 1H), 7.46 (d, *J* = 7.9 Hz, 2H), 7.38 (d, *J* = 8.0 Hz, 1H), 7.32 (d, *J* = 7.9 Hz, 1H), 7.24 (d, *J* = 7.9 Hz, 2H), 4.67 (s, 2H), 3.18 (d, *J* = 10.9 Hz, 2H), 2.96 (t, *J* = 7.4 Hz, 2H), 2.70-2.61 (m, 4H), 2.20 (d, *J* = 10.5 Hz, 2H), 1.68-1.64 (m, 2H), 1.52 (s, 3H), 1.34-1.33 (m, 7H), 0.90 (t, *J* = 6.2 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 142.70, 140.93, 137.11, 136.55, 134.40, 131.22, 129.05, 127.83, 126.91 125.39, 111.26, 79.58, 60.15, 55.44, 35.72, 32.43, 31.68, 31.30, 26.48, 25.00, 22.70, 14.19; HRMS (ESI): Calcd for $C_{26}H_{35}NO_2Cl$ $[M+H]^+$, 428.2351; found, 428.2365.

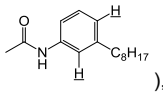
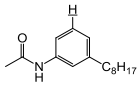
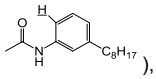
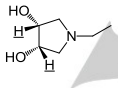
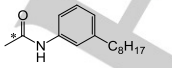
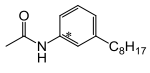
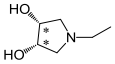
**(3R,4S)-1-(2-(3-Chloro-4'-pentyl-(1,1'-biphenyl)-4-yl)ethyl)pyrrolidine-3,4-diol (10h)**. Compound **10h** was prepared from **18h** as described in the preparation of compound 1**0a**. Yield: 74% as a white solid after column chromatography. $^1$H NMR (400 MHz, $CD_3OD$) δ 7.62-7.69 (m, 1H), 7.51-7.48 (m, 3H), 7.39-7.36 (m, 1H), 7.26-7.24 (m, 2H), 4.22-4.19 (m, 2H), 3.15-3.13 (m, 2H), 3.03-3.00 (m, 2H), 2.91-2.83 (m, 4H), 2.63 (t, *J* = 7.0 Hz, 2H), 1.68-1.62 (m, 2H), 1.40-1.35 (m, 4H), 0.93-0.89 (m, 3H); $^{13}$C NMR (100 MHz, $CD_3OD$) δ 143.96, 142.79, 137.94, 136.25, 135.35, 132.40, 130.08, 128.58, 127.70, 126.68, 71.45, 60.37, 57.62, 36.49, 32.60, 32.34, 23.59, 14.38; HRMS (ESI): Calcd for $C_{23}H_{31}NO_2Cl$ $[M+H]^+$, 388.2038; found, 388.2036.

**(3R,4S)-3,4-Di-*O*-isopropylidene-1-(2-(2-chloro-4-(*p*-tolylthio)-phenyl-1-yl)ethyl)pyrrolidine (18i)**. Compound **18i** was prepared from **17i** as described in the preparation of compound 1**8a**. Yield: 61% as a yellow oil after column chromatography (petroleum ether/ acetone 9:1) $^1$H NMR (400 MHz, $CDCl_3$) δ 7.52 (s, 1H), 7.43 (d, *J* = 8.3 Hz, 2H), 7.35-7.28 (m, 6H), 7.17 (d, *J* = 7.8 Hz, 2H), 4.66 (s, 2H), 3.17 (d, *J* = 11.0 Hz, 2H), 2.95 (t, *J* = 7.4 Hz, 2H), 2.68 (t, *J* = 8.0 Hz, 2H), 2.36 (s, 3H), 2.19 (d, *J* = 10.0 Hz, 2H), 1.51 (s, 3H), 1.32 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 140.13, 138.06, 137.78, 137.15, 137.02, 134.52, 132.75, 131.35, 130.91, 130.31, 129.93, 127.75, 127.60, 125.29, 111.25, 79.55, 60.12, 55.34, 32.41, 26.46, 24.98, 21.32; HRMS (ESI): Calcd for $C_{28}H_{31}NO_2SCl$ $[M+H]^+$, 480.1759; found, 480.1771.

**(3R,4S)-1-(2-(2-Chloro-4-(*p*-tolylthio)-phenyl-1-yl)ethyl)pyrrolidine-3,4-diol (10i)**. Compound **10i** was prepared from **18i** as described in the preparation of compound 1**0a**. Yield: 80% as a white solid after column chromatography. $^1$H NMR (400 MHz, $CD_3OD$) δ 7.62 (d, *J* = 1.8 Hz, 1H,  ), 7.52-7.49 (m, 3H), 7.40 (d, *J* = 8.0 Hz, 1H,  ), 7.31 (d, *J* = 8.1 Hz, 2H), 7.27 (d, *J* = 8.4 Hz, 2H), 7.20 (d, *J* = 8.0 Hz, 2H), 4.27 (s, 2H,  ), 3.17-3.13 (m, 2H), 3.08-2.98 (m, 6H), 2.34 (s, 3H,  ); $^{13}$C NMR (100 MHz, $CD_3OD$) δ 142.08, 139.42, 138.84, 138.54, 136.21, 135.48, 133.82, 132.53, 132.01, 131.24, 130.84, 128.61, 128.46, 126.70, 71.46, 60.41, 57.36, 49.64, 32.05,

21.13(  ); HRMS (ESI): Calcd for $C_{25}H_{27}NO_2SCl$ $[M+H]^+$, 440.1449; found, 440.1448.

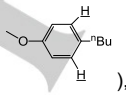
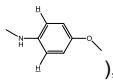
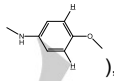
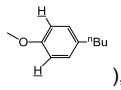
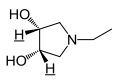
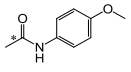
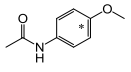
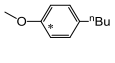
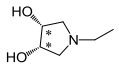
**2-((3aR,6aS)-2,2-Dimethyltetrahydro-5H-[1,3]dioxolo[4,5-c]pyrrol-5-yl)-*N*-(3-octylphenyl)acetamide(18j)**. Compound **18j** was prepared from **17j** as described in the preparation of compound 1**8a**. Yield: 58% as a light yellow solid after column chromatography (petroleum ether/ acetone 7:1) $^1$H NMR (400 MHz, $CDCl_3$) δ 9.26 (s, 1H), 7.40-7.35 (m, 2H), 7.22 (t, *J* = 7.7 Hz, 1H), 6.93 (d, *J* = 7.6 Hz, 1H), 4.71-4.68 (m, 2H), 3.26 (s, 2H), 3.19 (d, *J* = 11.4 Hz, 2H), 2.58 (t, *J* = 7.6 Hz, 2H), 2.36 (d, *J* = 10.2 Hz, 2H), 1.61-1.60 (m, 5H), 1.35 (s, 3H), 1.29-1.26 (m, 10H), 0.89-0.86 (m, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 168.30, 144.16, 137.73, 128.96, 124.47, 119.46, 116.78, 110.90, 79.46, 59.99, 57.23, 36.11, 32.03, 31.47, 29.62, 29.47, 29.38, 26.72, 24.46, 22.81, 14.25; HRMS (ESI): Calcd for $C_{23}H_{37}N_2O_3$ $[M+H]^+$, 389.2899; found, 389.2804.

**2-((3R,4S)-3,4-Dihydroxypyrrolidin-1-yl)-*N*-(3-octylphenyl)acetamide(10j)**. Compound **10j** was prepared from **18j** as described in the preparation of compound 1**0a**. Yield: 86% as a yellow solid after column chromatography. $^1$H NMR (400 MHz, $CD_3OD$) δ 7.44-7.42 (m, 2H,  ), 7.21 (t, *J* = 7.7 Hz, 1H,  ), 6.94 (d, *J* = 7.5 Hz, 1H,  ), 4.34 (s, 2H,  ), 3.84 (s, 2H,  ), 3.21 (br, 2H), 2.57 (t, *J* = 7.6 Hz, 2H), 1.99 (br, 2H), 1.59-1.57 (m, 2H), 1.30-1.27 (m, 10H), 0.88 (t, *J* = 6.6 Hz, 3H); $^{13}$C NMR (100 MHz, $CD_3OD$) δ 168.10(  ), 144.92(  ), 138.88, 129.72, 125.79, 121.20, 118.64, 71.83(  ), 60.19, 59.80, 36.87, 32.97, 32.54, 30.52, 30.34, 30.28, 23.66, 14.43; HRMS (ESI): Calcd for $C_{20}H_{33}N_2O_3$ $[M+H]^+$, 349.2486; found, 349.2498.

**2-((3aR,6aS)-2,2-Dimethyltetrahydro-5H-[1,3]dioxolo[4,5-c]pyrrol-5-yl)-*N*-(3-hexylphenyl)-acetamide (18k)**. Compound **18k** was prepared from **17k** as described in the preparation of compound 1**8a**. Yield: 77% as a yellow solid after column chromatography (petroleum ether/ acetone 7:1). $^1$H NMR (400 MHz, $CDCl_3$) δ 9.26 (s, 1H), 7.40 (s, 1H), 7.37 (d, *J* = 8.0 Hz, 1H), 7.22 (t, *J* = 7.7 Hz, 1H), 6.93, (d, *J* = 7.6 Hz, 1H), 4.71-4.67 (m, 2H), 3.25 (s, 2H), 3.19 (d, *J* = 10.9 Hz, 2H), 2.56 (t, *J* = 7.6 Hz, 2H), 2.36 (d, *J* = 10.2 Hz, 2H), 1.61-1.56 (m, 5H), 1.35-1.27 (m, 9H), 0.88 (t, *J* = 6.6 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 168.34, 144.14, 137.72, 128.95, 124.45, 119.44, 116.76, 110.86, 79.46, 59.97, 57.21, 36.07, 31.84, 31.40, 29.10, 26.71, 24.45, 22.70, 14.22; HRMS (ESI): Calcd for $C_{21}H_{33}N_2O_3$ $[M+H]^+$, 361.2486; found, 361.2487.

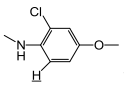
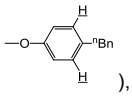
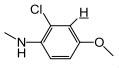
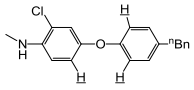
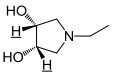
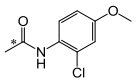
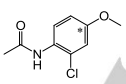
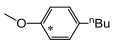
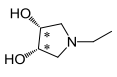
**2-((3R,4S)-3,4-Dihydroxypyrrolidin-1-yl)-*N*-(3-hexylphenyl)acetamide (10k)**. Compound **10k** was prepared from **18k** as described in the preparation of compound 1**0a**. Yield: 86% as a light yellow viscous oil after column chromatography. $^1$H NMR (400 MHz, $CD_3OD$) δ 7.44-7.42 (m, 2H), 7.20 (t, *J* = 7.6 Hz, 1H), 6.66 (d, *J* = 7.6 Hz, 1H), 4.27-4.22 (m, 2H), 3.40 (s, 2H), 2.92-2.86 (m, 4H), 2.56 (t, *J* = 7.6 Hz, 2H), 1.60-1.55 (m, 2H), 1.32-1.29 (m, 6H), 0.88 (t, *J* = 6.4 Hz, 3H); $^{13}$C NMR (100 MHz, $CD_3OD$) δ 171.06, 144.83, 139.02, 129.64, 125.65, 121.35, 118.78, 72.26, 60.62, 60.36, 36.90, 32.82, 32.54, 29.99, 23.62, 14.43; HRMS (ESI): Calcd for $C_{18}H_{29}N_2O_3$ $[M+H]^+$, 321.2173; found, 321.2178.

***N*-(4-(4-Butylphenoxy)phenyl)-2-((3aR,6aS)-2,2-dimethyltetrahydro-5H-[1,3]dioxolo[4,5-c]pyrrol-5-yl)acetamide (18l)**. Compound **18l** was prepared from **17l** as described in the preparation of compound 1**8a**. Yield: 92% as a light yellow oil after column chromatography (petroleum ether/ acetone 10:1). $^1$H NMR (400 MHz, $CDCl_3$) δ 9.26 (s, 1H), 7.52 (d, *J* = 8.8 Hz, 2H), 7.12 (d, *J* = 8.3 Hz, 2H), 6.97 (d, *J* = 8.8 Hz, 2H), 6.89 (d, *J* = 8.4 Hz, 2H), 4.68 (s, 2H), 3.26 (s, 2H), 3.18 (d, *J* = 11.0 Hz, 2H), 2.58 (t, *J* = 7.6 Hz, 2H), 2.35 (d, *J* = 10.2 Hz, 2H), 1.62-1.55 (m, 5H), 1.38-1.31 (m, 5H), 0.93 (t, *J* = 7.3 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 168.25, 155.34, 153.83, 137.75, 133.07, 129.57, 120.84, 119.35, 118.47, 110.72, 79.33, 59.85, 56.96, 34.92, 33.83, 29.30, 26.66, 24.31, 22.36, 14.02; HRMS (ESI): Calcd for $C_{25}H_{33}N_2O_4$ $[M+H]^+$, 425.2435; found, 425.2431.

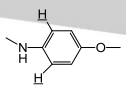
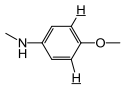
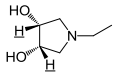
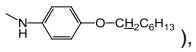
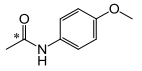
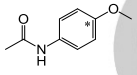
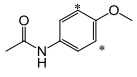
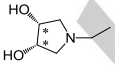
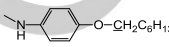
***N*-(4-(4-Butylphenoxy)phenyl)-2-((3R,4S)-3,4-dihydroxypyrrolidin-1-yl)acetamide (10l)**. Compound **10l** was prepared from **18l** as described in the preparation of compound 1**0a.** Yield: 74% as a light yellow solid after column chromatography. $^1$H NMR (400 MHz, $CD_3OD$) δ 7.57-7.53 (m, 2H,  ), 7.14-7.12 (m, 2H,  ), 6.91-6.89 (m, 2H,  ), 6.87-6.85 (m, 2H,  ), 4.28 (br, 2H,  ), 3.57 (s, 2H,  ), 3.02 (br, 4H), 2.57 (t, *J* = 7.6 Hz, 2H), 1.61-1.53 (m, 2H), 1.39-1.30 (m, 2H), 0.93 (t, *J* = 7.3 Hz, 3H); $^{13}$C NMR (100 MHz, $CD_3OD$) δ 169.72(  ), 156.55(  ), 155.65(  ), 139.08, 134.27, 130.68, 123.04, 119.77, 119.63, 72.08(  ), 60.44, 60.14, 35.84, 35.05, 23.29, 14.30; HRMS (ESI): Calcd for $C_{22}H_{29}N_2O_4$ $[M+H]^+$, 385.2122; found, 385.2113.

***N*-(4-(4-Butylphenoxy)-2-chlorophenyl)-2-((3aR,6aS)-2,2-dimethyltetrahydro-5H-[1,3]dioxolo[4,5-c]pyrrol-5-yl)acetamide (18m)**. Compound **18m** was prepared from **17m** as described in the preparation of compound 1**8a**. Yield: 98% as a yellow solid after column chromatography (petroleum ether/ acetone 10:1). $^1$H NMR (400 MHz, $CDCl_3$) δ 9.49 (s, 1H), 8.26 (d, *J* = 9.0 Hz, 1H), 7.15 (d, *J* = 8.4 Hz, 2H), 7.02 (d, *J* = 2.7 Hz, 1H), 6.94-6.90 (m, 3H), 4.72-4.70 (m, 2H), 3.31-3.28 (m, 4H), 2.59 (t, *J* = 7.7 Hz, 2H), 2.35 (d, *J* = 10.2 Hz, 2H), 1.63-1.55 (m, 5H), 1.41-1.33 (m, 5H), 0.93 (t, *J* = 7.3 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 168.41, 154.61, 154.19, 138.56, 129.82, 129.75, 124.60, 123.00, 119.13, 118.98, 117.67, 110.99, 79.43, 60.39, 58.78, 35.04,

33.87, 26.27, 24.18, 22.45, 14.09; HRMS (ESI): Calcd for $C_{25}H_{32}N_2O_4Cl$ $[M+H]^+$, 459.2046; found, 459.2044.

***N*-(4-(4-Butylphenoxy)-2-chlorophenyl)-2-((3R,4S)-3,4-dihydroxypyrrolidin-1-yl)acetamide (10m)**. Compound **10m** was prepared from **18m** as described in the preparation of compound 1**0a.** Yield: 71% as white solid after column chromatography. $^1$H NMR (400 MHz, $CD_3OD$) δ 7.84 (d, *J* = 8.9 Hz, 1H,  ), 7.16 (d, *J* = 8.3 Hz, 2H,  ), 6.99 (d, *J* = 2.6 Hz, 1H,  ), 6.90-6.85 (m, 3H,  ), 4.26 (s, 2H,  ), 3.42 (s, 2H,  ), 2.96 (br, 2H), 2.88-2.86 (m, 2H), 2.58 (t, *J* = 7.6 Hz, 2H), 1.61-1.53 (m, 2H), 1.39-1.30 (m, 2H), 0.92 (t, *J* = 7.3 Hz, 3H); $^{13}$C NMR (100 MHz, $CD_3OD$) δ 171.73(  ), 156.99(  ), 155.50(  ), 140.04, 130.89, 130.22, 128.39, 126.68, 120.26, 119.77, 118.05, 72.17(  ), 60.92, 60.08, 35.83, 34.89, 23.26, 14.27; HRMS (ESI): Calcd for $C_{22}H_{28}N_2O_4Cl$ $[M+H]^+$, 419.1733; found, 419.1732.

***N*-(2-Chloro-4-(heptyloxy)phenyl)-2-((3aR,6aS)-2,2-dimethyltetrahydro-5H-[1,3]dioxolo[4,5-c]pyrrol-5-yl)acetamide (18n)**. Compound **18n** was prepared from **17n** as described in the preparation of compound 1**8a.** Yield: 79% as a light yellow oil after column chromatography (petroleum ether/ acetone 2.5:1). $^1$H NMR (400 MHz, $CDCl_3$) δ 9.16 (s, 1H), 7.46 (d, *J* = 8.9 Hz, 2H), 6.86 (d, *J* = 8.9 Hz, 2H), 4.70-4.67 (m, 2H), 3.93 (t, *J* = 6.6 Hz, 2H), 3.25 (s, 2H), 3.18 (d, *J* = 11.3 Hz, 2H), 2.35 (d, *J* = 10.2 Hz, 2H), 1.80-1.73 (m, 2H), 1.59 (s, 3H), 1.48-1.40 (m, 2H), 1.35-1.24 (m, 9H), 0.89 (t, *J* = 6.6 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 168.05, 155.95, 130.94, 120.96, 115.00, 110.87, 79.47, 68.45, 60.01, 57.17, 31.91, 29.41, 29.19, 26.75, 26.12, 24.47, 22.74, 14.21; HRMS (ESI): Calcd for $C_{22}H_{35}N_2O_4$ $[M+H]^+$, 391.2592; found, 391.2592.

***N*-(2-Chloro-4-(heptyloxy)phenyl)-2-((3R,4S)-3,4-dihydroxypyrrolidin-1-yl)acetamide (10n)**. Compound **10n** was prepared from **18n** as described in the preparation of compound 1**0a.** Yield: 90% as a light yellow solid after column chromatography. $^1$H NMR (400 MHz, $CD_3OD$) δ 7.49-7.47 (m, 2H,  ), 6.88-6.86 (m, 2H,  ), 4.28 (br, 2H,  ), 3.94 (t, *J* = 10.4 Hz, 2H,  ), 3.53 (s, 2H,  ), 3.01-2.98 (m, 2H), 2.95-2.94 (m, 2H), 1.79-1.72 (m, 2H), 1.50-1.43 (m, 2H), 1.41-1.33 (m, 6H), 0.91 (t, *J* = 6.7 Hz, 3H); $^{13}$C NMR (100 MHz, $CD_3OD$) δ 170.16(  ), 157.58(  ), 131.80, 123.07, 115.57(  ), 72.18(  ), 69.15(  ), 60.42, 59.39, 32.88, 30.36, 30.13, 27.05, 23.58, 14.41; HRMS (ESI): Calcd for $C_{19}H_{31}N_2O_4$ $[M+H]^+$, 351.2279; found, 351.2280.

**Biology**

All laboratory animal experiments were performed according to the national guidelines and approved by the Institutional Animal Care and Use Committee of Peking University.

**Preparation of mouse splenocytes suspension**

Splenocytes suspensions were prepared from male BALB/c mouse. Mouse splenocytes were plated on 96-well microplates at a density of $5\times10^5$ cells/well and cultured in RPMI-1640 media (Hyclone) containing 10% fetal bovine serum (FBS), 2.5 μg/mL concanavalin A alone or along with 5 μM of synthetic iminosugar compounds at 37 °C, 5% $CO_2$ for 48 h.

**Proliferation assays**

Proliferation of the mouse splenocytes was assayed using the CCK-8 reduction method. CCK-8 (20 mL) was added to each well and the plates were incubated for 2 h at 37 °C. Optical density was measured using a Microplate Reader at 450 nm. All data were presented as mean ± SEM.

**Cytokine measurement**

The 96-well microplates were incubated for 48 h in 5% $CO_2$ at 37 °C, and the plates were centrifuged at 4 °C, 1500×g for 15 min to precipitate the cells. The supernatant was taken, and stored at −20 °C before the measurement of the cytokines. The samples, which had been frozen, were thawed to room temperature before the measurements of IL-4 and INF-γ were taken. The amounts of cytokines were measured with enzyme-linked immunosorbent assay (IL-4 ELISA kit, Bender MedSystems, Vienna, Austria; INF-γ ELISA kit, San Diego, USA) procedures according to the manufacturer's directions.

## Acknowledgements

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**Keywords:** iminosugar; immunosuppressant; *N*-alkylation; synthesis

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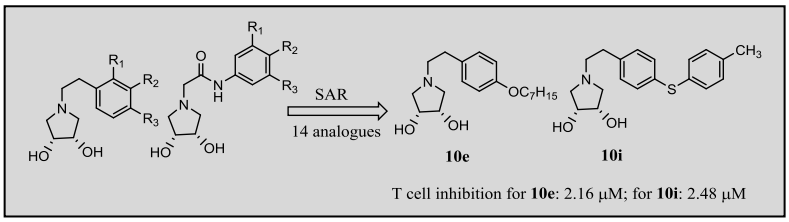
## Entry for the Table of Contents




A series of *N*-substituted iminosugar derivatives were designed and synthesized. The immunosuppressive effects evaluated by CCK-8 assay revealed that iminosugars **10e** and **10i** exhibited the strongest inhibitory effect on mouse splenocyte proliferation ($IC_{50}$ = 2.16 and 2.48 μM, respectively).