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Syntheses of Arabinose-derived Pyrrolidine Catalysts and Their Applications in Intramolecular Diels-Alder Reactions

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Six chiral hydroxylated pyrrolidine catalysts were synthesized from commercially available D-arabinose in seven steps. Various aromatic substituents α to the amine can be introduced readily by a Grignard reaction, which enables facile optimization of the catalyst performance. The stereoselectivities of these catalysts have been assessed by comparing with those of MacMillan's imidazolidinone on a known intramolecular Diels-Alder (IMDA) reaction of a triene. Two additional IMDA reactions of symmetrical dienals with concomitant desymmetrisation further established the potential use of these novel amine catalysts. These pyrrolidines are valuable catalysts for other synthetic transformations.

Introduction

Enantioselective organocatalysis, which signifies the use of small chiral organic molecules to promote different chemical transformations in a stereoselective manner, is a research area that has received widespread attention over the past decade.¹ Nowadays, organocatalysis has become a vast and interconnected field of catalysis, which produces a large volume of research work with intriguing prospectives. Organocatalysis has established itself as a vital role in asymmetric catalysis, complementing enzymes and organometallic catalysis.²

Among the different classes of organocatalysis, aminocatalysis was first reckoned to have a general catalysis concept. Two representative classes of chiral amine catalysts are MacMillan's imidazolidinone organocatalysts (**1**) and Jørgensen's diarylprolinol silyl ether organocatalysts (**2**) (Figure 1). MacMillan's catalysts were synthesized from L-phenylalanine^{3a} and the diarylprolinol ethers were derived from L-proline⁵; both of these catalyst classes have demonstrated impressive results in a large array of chemical transformations, including Diels-Alder reaction,^{3a,6,7} aldol reaction,^{8a} epoxidation,⁹ cyclopropanation,¹⁰ enal hydrogenation,¹¹ Friedel-Crafts alkylation,¹² Mannich reaction,^{8b} Michael reaction,¹³ 1,3-dipolar cycloaddition,^{8c} domino reaction¹⁴ and halogenation.¹⁵

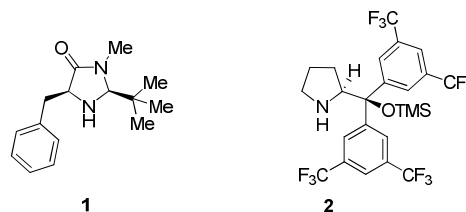
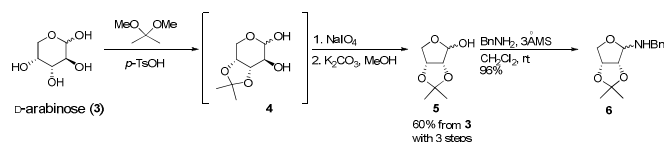


Fig. 1 Chiral amine catalysts.

Inspired by the powerful capabilities of aminocatalysis, our group has initiated a project to develop new chiral pyrrolidines with a mono-aryl group that would complement the existing diarylprolinol ether and imidazolidinone catalysis. With a glance of the aforementioned amine catalysts, we believe that modification of MacMillan's catalysts should not be easily performed on the phenyl group of the amino acid; whereas modification on proline was possible on the acid functionality and afforded a series of diaryl prolinol derivatives. However, reactions catalyzed by diaryl prolinols could be sluggish due to the bulky diaryl substituents and the corresponding mono-aryl prolinol derivatives are not readily accessible. As a result, the feature in our catalyst design is that the aryl group can be easily modified in adjusting the electronic or steric demand of the blocking group, via different substituents on the phenyl ring.

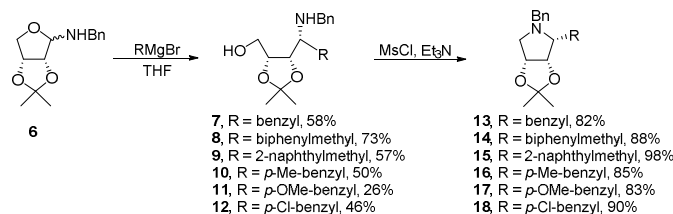
Results and Discussion

D-Arabinose was conveniently chosen as the starting material because of its built-in chirality and its ready commercial availability in large quantities for both enantiomers. The synthetic scheme is shown below (Scheme 1):



Scheme 1 Synthesis of hemiaminal 6.

The hydroxyl groups at C-3,4 of D-arabinose (**3**) were first selectively protected by kinetic acetonation. The 1,2-diol unit underwent glycol cleavage oxidation and the subsequent basic hydrolysis smoothly generated 2,3-*O*-isopropylidene-D-erythrose (**5**) with 60% overall yield in three steps. Lactol **5** was then converted into hemiaminal **6** by reacting with benzylamine in the presence of 3Å molecular sieves prior to Grignard reaction. Such conversion was made because direct Grignard reaction on lactol **5** resulted in poor regio- and diastereoselectivity. In contrast, Grignard reaction of the common intermediate hemiaminal **6** smoothly furnished amines **7-12** regio and stereospecifically. Mesylation of the free alcohol followed by facile intramolecular substitution reaction gave tertiary amines **13-18** in good yields. (Scheme 2).



Scheme 2 Syntheses of protected pyrrolidines.

The stereochemical outcome of the Grignard addition can be rationalized by an α -chelation model, where the metal center is chelated with the oxygen and nitrogen functionalities, β attack is more favourable to give amines **7-12** due to steric hindrance of the isopropylidene ring. Such a stereospecific addition on imine not only provided the desired stereochemistry, but also a more accessible and simple approach to introduce the mono-aryl group on the catalyst without any rearrangement problem (Figure 2).

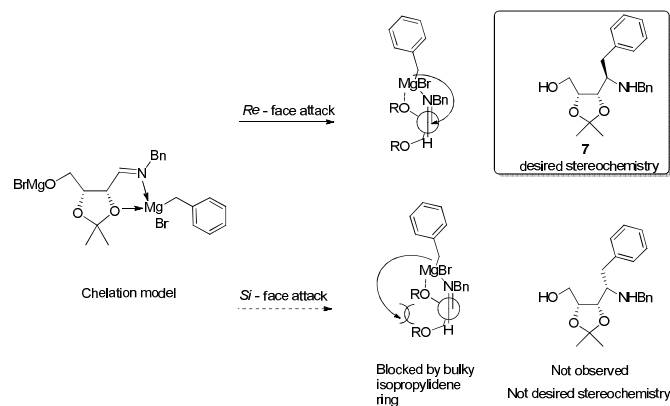
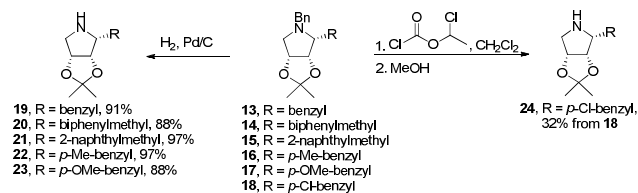


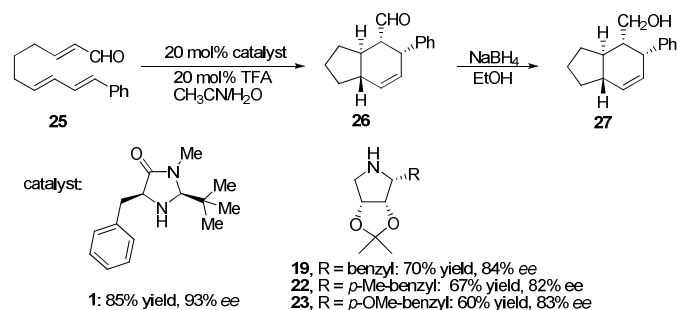
Fig. 2 Proposed Grignard addition pathway.

Finally, the *N*-benzyl group of the amines **13-17** was deprotected by hydrogenolysis in the presence of 10% Pd-on-charcoal to give the chiral pyrrolidine catalysts **19-23**. Amine **18** on the other hand, underwent dehalogenation and an alternative strategy using α -chloroethyl chloroformate¹⁶ was employed to obtain the desired amine catalyst **24** (Scheme 3).



Scheme 3 Syntheses of pyrrolidine catalysts 19-24.

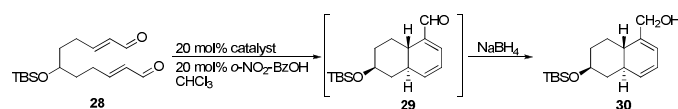
With the chiral pyrrolidine catalysts in hand, we first compared them with MacMillan's imidazolidinone **1**, following his published enantioselective intramolecular Diels-Alder reaction (IMDA) (Scheme 4).⁶ The results indicated that although the enantioselectivities of our amine catalysts were not as superior as those of MacMillan's catalyst, satisfactory enantiocontrol could be attained.



Scheme 4 Chiral amine catalysed asymmetric IMDA reactions.

On the other hand, Hong¹⁷ and Christmann¹⁸ have applied Jørgensen's catalyst in enantioselective IMDA reaction of dienals to create bicyclic ring systems. In view of the potential of functionalized bicyclic ring systems, we designed and synthesized two hydroxylated dienals and applied our amine catalysts in enantioselective IMDA reactions with concomitant desymmetrization. Dienals **28** and **31** were prepared from ethyl formate and ethyl glycolate via standard transformations, respectively (see Supporting Information for details). Several solvents and co-acids were evaluated and it was found that chloroform and *o*-nitrobenzoic acid gave the best results. The results of the IMDA reactions are shown below:

Table 1. Chiral Pyrrolidine catalysed Intramolecular Diels-Alder Reactions of dienal **28** with concomitant desymmetrization.



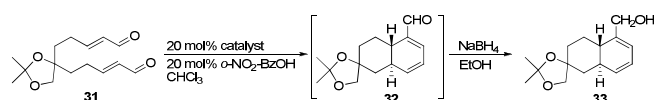
Entry ^a	Catalyst	R	Temp	Reaction Time	Yield (%) ^b	<i>ee</i> (%) ^c
1	19	benzyl	rt	20 h	11	90
2	20	biphenylmethyl	rt	21 h	10	86
3	21	2-naphthylmethyl	rt	16 h	9	90
4	22	<i>p</i> -Me-benzyl	rt	20 h	13	87
5	23	<i>p</i> -OMe-benzyl	rt	20 h	9	88
6	24	<i>p</i> -Cl-benzyl	rt	20 h	12	87

^a All IMDA reactions were carried out at 0.1M.

^b Isolated yield.

^c Enantioselectivity was determined by HPLC using a chiral column.

Table 2. Chiral Pyrrolidine catalysed Intramolecular Diels-Alder Reactions of dienal **31** with concomitant desymmetrization.



Entry ^a	Catalyst	R	Temp	Reaction Time	Yield (%) ^a	<i>ee</i> (%) ^b
1	19	benzyl	rt	9 h	16	82
2	20	biphenylmethyl	rt	9 h	16	77
3	21	2-naphthylmethyl	rt	9 h	15	81
4	22	<i>p</i> -Me-benzyl	rt	16 h	20	80
5	23	<i>p</i> -OMe-benzyl	rt	8 h	17	77
6	24	<i>p</i> -Cl-benzyl	rt	8 h	18	78

^a All IMDA reactions were carried out at 0.1M.

^b Isolated yield.

^c Enantioselectivity was determined by HPLC using chiral column.

Among the six amine catalysts screened, amines **19** (R= benzyl) and **21** (R= 2-naphthylmethyl) displayed comparatively better

chiral induction in both IMDA reactions, despite the generally poor chemical yields. The low yields are attributed to the instability of both the starting material and the cycloadduct in the IMDA reactions, as both were found decomposing before reaction completion.

Vinylogous enamine activated IMDA reactions are assumed and the proposed catalytic cycle is illustrated in Figure 3 using hydroxylated dienal **28** and amine **19** as an example. Amine **19** would condense with an aldehyde function in **28** to form enamine **34**, via a *trans-trans* iminium ion, with the carbon chain pointing away from the bulky benzyl group in order to minimize steric repulsion. It is expected that the π -system of the enamine is relatively open at the α -face and thus is ready for *endo*-approach of the enol moiety from the bottom face by steric control. β -Elimination of the cycloadduct **35** gives a thermodynamically stable dienal system **29** and liberates amine **19**. It is reasonable to rationalize that the amine catalyst would assist this elimination via the formation of an iminium ion with the remaining aldehyde group either before or after the IMDA reaction.

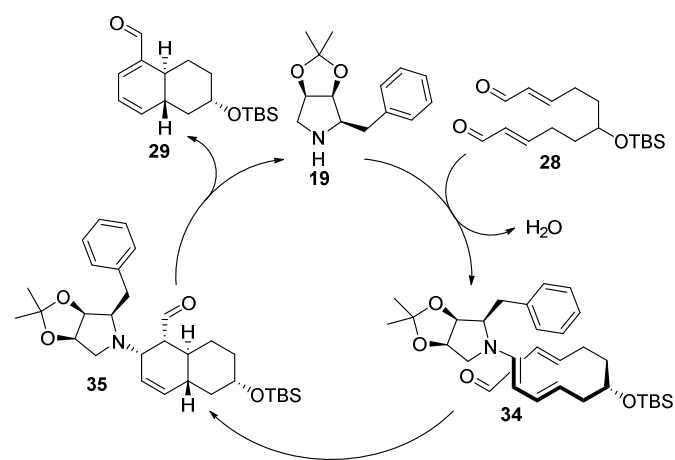


Fig. 3. Proposed catalytic cycle of

asymmetric IMDA reaction of **28**.

Conclusion

To summarize, the extraordinary potential of the new pyrrolidine catalysts **19-24** should not be dismissed just because of the low yields obtained from the current IMDA reactions of dienals. Facile modification of the aromatic unit and the ready availability of both enantiomers of the pyrrolidine catalysts provide a very flexible and practical platform to tackle amine catalyzed reactions. Application of our amine catalysts to different reaction types involving enamine and iminium ion activation modes is underway.

Experimental section

General Information

Melting points were measured with a Reichert apparatus in Celsius degrees and are uncorrected. Optical rotations were obtained operating at 589nm. Infrared (IR) spectra were recorded as thin films on potassium bromide discs. Nuclear magnetic resonance (NMR) spectra were measured with at 400.19 MHz (^1H) or at 100.62 MHz (^{13}C) in CDCl_3 solutions, unless stated otherwise. All chemical shifts were recorded in ppm relative to tetramethylsilane ($\delta = 0.0$). Spin-spin coupling constants (J value) recorded in Hz were measured directly from the spectra. MS and HRMS were measured on a ESI-MS instrument with a magnetic sector analyzer. All reactions were monitored by analytical thin-layer chromatography (TLC) on aluminium-precoated plates of silica gel 60 F254 with detection by spraying with 5% (w/v) dodecamolybdophosphoric acid in ethanol or 5% (w/v) ninhydrin in ethanol, and subsequent heating. Silica gel 60 (230-400 mesh) was used for flash chromatography. All reagents and solvents were general reagent grade unless otherwise stated. DMF was dried by magnesium sulfate, filtered, and the filtrate was then distilled under reduced pressure. THF was freshly distilled from Na/benzophenone ketyl under nitrogen. Et_2O was freshly distilled from K/benzophenone ketyl under nitrogen. Dichloromethane and chloroform were freshly distilled from P_2O_5 under nitrogen. Other reagents were purchased from commercial suppliers and were used without purification.

General procedure for glycol cleavage reaction. NaIO_4 (3 eq.) was dissolved in a minimum amount of hot water ($\sim 80^\circ\text{C}$) and to this solution was added silica gel (230–400 mesh, 10 \times weight of diol) with vigorous swirling and shaking. The mixture was suspended in CH_2Cl_2 and then a solution of diol (1 eq.) in CH_2Cl_2 was added. After vigorous stirring at room temperature for 1 h, the mixture was filtered. The filtrate was concentrated under reduced pressure to give the aldehyde product.

Generation of benzylmagnesium bromide/chloride. To a suspension of magnesium powder (150 mmol) in THF (50 mL) was added 1,2-dibromoethane (0.36 mL) and the mixture was stirred at room temperature for 15 min. A solution of benzyl halide (50.0 mmol) in THF (50 mL) was added dropwise to the mixture at a rate to maintain a gentle reflux of the THF. After the addition of the benzyl halide solution, the mixture was heated under reflux for 2h and then cooled down for use. The concentration of the benzylmagnesium bromide/ chloride solution generated was around 0.5 M.

Lactol 5. To a milky suspension of dry D-arabinose **3** (5.55 g, 37.0 mmol) in DMF (50 mL) were added 2,2-dimethoxypropane (13.6 mL, 110 mmol) and TsOH (629 mg, 3.70 mmol) at room temperature. The solution became clear

after being stirred at room temperature for 15 min. The resultant solution was stirred at room temperature for another 18 h. The reaction was quenched by dropwise addition of Et_3N until pH \sim 7 (test by pH paper). The solution was concentrated under reduced pressure to afford the crude **4**. Following by the glycol cleavage procedure, the crude **4** was converted to colourless oil. The powdered K_2CO_3 (2.66 g, 19.2 mmol) was added to the solution of crude mixture in MeOH (50 mL). The mixture was stirred at room temperature for 24 h. The resultant mixture was filtered through a pad of silica gel that was eluted with Et_2O . Concentration of the filtrate followed by flash chromatography (Hexane: Et_2O , 3:2) yielded lactol **5** (3.54 g, 60%) as a colourless oil: $[\alpha]_{\text{D}}^{20} -59.4$ (c 2.45, CHCl_3) {lit.43 $[\alpha]_{\text{D}}^{25} -79.3$ (c 0.925, CHCl_3)}; Rf 0.3 (Hexane: Et_2O , 1:2); IR (thin film) 3438, 2986, 2940, 1378, 1214, 1071, 989, 856 cm^{-1} ; ^1H NMR (major anomer) δ 1.30 (3H, s), 1.45 (3H, s), 3.37 (1H, br s), 3.98–4.06 (2H, m), 4.55 (1H, d, $J = 5.9$ Hz), 4.82 (1H, dd, $J = 5.8, 3.7$ Hz), 5.39 (1H, s); ^{13}C NMR δ 25.0, 26.5, 72.2, 80.2, 85.4, 102.1, 112.6; MS (ESI) m/z (relative intensity) 183 ($[\text{M} + \text{Na}]^+$, 100); HRMS (ESI) calcd for $\text{C}_7\text{H}_{12}\text{O}_4$ $[\text{M} + \text{Na}]^+$ 183.0628, found 183.0831.

Imine 6. To a solution of lactol **5** (5.74 g, 35.8 mmol) in CH_2Cl_2 (10 mL) were added BnNH_2 (39 mL, 358 mmol) and 3 \AA molecular sieves (ca. 22 g) at room temperature. The reaction mixture was stirred at room temperature for 24 h until the disappearance of the starting material as shown on TLC. The mixture was filtered and the residue was washed with EtOAc. Concentration of the filtrate followed by flash column chromatography (hexane:EtOAc, 3:1) produced imine **6** (8.60 g, 96%) as a white solid: mp 58–59 $^\circ\text{C}$; $[\alpha]_{\text{D}}^{20} -34.0$ (c 2.22, CHCl_3); Rf 0.33 (hexane:EtOAc, 1:1); IR (thin film) 3673, 3456, 3269, 3028, 2932, 2858, 1461, 1376, 1270, 1209, 1102, 1057, 992, 859, 702 cm^{-1} ; ^1H NMR δ 1.31 (0.87H, s), 1.33 (3H, s), 1.5 (3.8H, s), 3.42 (1H, dd, $J = 11, 3.2$ Hz), 3.77 (0.29H, d, $J = 13.3$ Hz), 3.89 (0.29H, d, $J = 13.3$ Hz), 3.93–3.99 (2.58H, m), 4.15 (1H, d, $J = 13.3$ Hz), 4.29 (1H, d, $J = 3.3$ Hz), 4.40 (0.29 H, d, $J = 6$ Hz), 4.50 (1H, dd, $J = 6, 3.5$ Hz), 4.68 (1H, dd, $J = 6, 3.6$ Hz), 4.77–4.82 (0.58 H, m), 7.23–7.41 (6.45H, m); ^{13}C NMR δ 24.5, 24.8, 25.9, 26.3, 49.2, 50.1, 68.7, 70.5, 79.2, 79.8, 80.5, 85.2, 91.3, 94.4, 111.9, 112.3, 128.2, 128.2, 128.2, 128.4, 139.6, 139.9; MS (ESI) m/z (relative intensity) 250 ($[\text{M}]^+$, 100), 251 (23), 252 (2); HRMS (ESI) calcd for $\text{C}_{14}\text{H}_{19}\text{NO}_3$ $[\text{M}]^+$ 250.1438, found 250.1440.

Amine 7 (R=benzyl). To a stirred solution of a 0.5M THF solution of benzylmagnesium bromide (4.7 mL, 2.34 mmol) was added imine **6** (56.2 mg, 0.225 mmol) in dry THF (4.3 mL) dropwise at -20°C under N_2 . After the addition, the mixture was allowed to rise to room temperature and stirred for a further 13 h. The mixture was quenched with saturated NH_4Cl solution and the aqueous phase was extracted with EtOAc (3 \times 20 mL). The combined organic extracts were dried over anhydrous MgSO_4 , and filtered. The filtrate was concentrated under reduced pressure and the residue was purified by flash chromatography (hexane: Et_2O , 1:1) to afford amine **7** (44.5 mg,

58%) as a colourless oil: $[\alpha]_{\text{D}}^{20}$ -34.6 (c 1.98, CHCl₃); Rf 0.22 (hexane:Et₂O, 1:2); IR (thin film) 3678, 3653, 3457, 3270, 3063, 3028, 2985, 2930 1495, 1455, 1214, 1061, 745 cm⁻¹; ¹H NMR δ 1.34 (3H, s), 1.53 (3H, s), 2.77 (1H, dd, *J* = 13.1, 9.7 Hz), 3.03 (1H, ddd, *J* = 9.6, 4.6, 1.4 Hz), 3.35 (1H, dd, *J* = 13.1, 4.6 Hz), 3.56 (1H, dd, *J* = 12.8, 2.2 Hz), 3.73 (1H, dd, *J* = 12.8, 4.9 Hz), 3.88 (1H, d, *J* = 12.3 Hz), 3.96–4.00 (1H, m), 4.06 (1H, d, *J* = 12.3 Hz), 4.15 (1H, dd, *J* = 7.2, 1.5 Hz), 7.19–7.38 (10H, m); ¹³C NMR δ 24.7 (CH₃), 26.7 (CH₃), 37.3 (CH₂), 50.5 (CH₂), 56.5 (CH), 60.6 (CH₂), 76.3 (CH), 77.7 (CH), 107.5 (C), 126.5 (CH), 127.6 (CH), 128.6 (CH), 128.7 (CH), 128.7 (CH), 129.2 (CH), 138.1 (C), 138.6 (C); MS (ESI) *m/z* (relative intensity) 342 ([M+H]⁺, 100), 343 (24), 344 (4); HRMS (ESI) calcd for C₂₁H₂₇NO₃ [M+H]⁺ 342.2064, found 342.2059.

Amine 8 (R=biphenylmethyl). Following the general procedure for generation of benzylic zinc reagent, the 4-(bromomethyl)biphenyl (850 mg, 3.44 mmol) was converted into the biphenylmethyl zinc reagent at 25 °C in 2h. To a stirred solution of a 0.31M THF solution of biphenylmethyl zinc bromide (11.1 mL, 3.44 mmol) was added imine **6** (87.7 mg, 0.336 mmol) in dry THF (29 mL) dropwise at -20 °C under N₂. After the addition, the mixture was allowed to rise to room temperature and stirred for a further 24 h. The mixture was quenched with saturated NH₄Cl solution and the aqueous phase was extracted with EtOAc (3 × 20 mL). The combined organic extracts were dried over anhydrous MgSO₄, and filtered. The filtrate was concentrated under reduced pressure and the residue was purified by flash chromatography (hexane:Et₂O, 1:1) to afford amine **8** (102 mg, 73%) as a colourless oil: $[\alpha]_{\text{D}}^{20}$ -48.6 (c 2.11, CHCl₃); R_f 0.15 (hexane:Et₂O, 1:2); IR (thin film) 3677, 3653, 3423, 3205, 3026, 2984, 2931, 1486, 1451, 1375, 1248, 1214, 1137, 1055, 754 cm⁻¹; ¹H NMR δ 1.36 (3H, s), 1.55 (3H, s), 2.81 (1H, dd, *J* = 13.0, 9.8 Hz), 3.06 (1H, ddd, *J* = 9.7, 4.6, 1.2 Hz), 3.39 (1H, dd, *J* = 13.1, 4.5 Hz), 3.58 (1H, dd, *J* = 12.8, 2.0 Hz), 3.75 (1H, dd, *J* = 12.8, 4.9 Hz), 3.90 (1H, d, *J* = 12.3 Hz), 3.99–4.02 (1H, m), 4.09 (1H, d, *J* = 12.3 Hz), 4.20 (1H, dd, *J* = 7.2, 1.4 Hz), 7.28–7.39 (8H, m), 7.44–7.48 (2H, m), 7.56–7.62 (4H, m); ¹³C NMR δ 24.8 (CH₃), 26.7 (CH₃), 37.0 (CH₂), 50.6 (CH₂), 56.6 (CH), 60.6 (CH₂), 76.4 (CH), 77.8 (CH), 107.6 (C), 126.9 (CH), 127.3 (CH), 127.4 (CH), 127.6 (CH), 128.7 (CH), 128.7 (CH), 128.8 (CH), 129.7 (CH), 137.7 (C), 138.2 (C), 139.4 (C), 140.7 (C); MS (ESI) *m/z* (relative intensity) 418 ([M+H]⁺, 100), 419 (35), 420 (5); HRMS (ESI) calcd for C₂₇H₃₁NO₃ [M+H]⁺ 418.2377, found 418.2369.

Amine 9 (R=2-naphthylmethyl). To a stirred solution of a 0.25M Et₂O solution of 2-naphthylmethylmagnesium bromide (146 mL, 36.5 mmol) was added imine **6** (910 mg, 3.65 mmol) in dry THF (20 mL) dropwise at -20 °C under N₂. After the addition, the mixture was allowed to rise to room temperature and stirred for a further 24 h. The mixture was quenched with saturated NH₄Cl solution and the aqueous phase was extracted with EtOAc (3 × 50 mL). The combined organic extracts were dried over anhydrous MgSO₄, and filtered. The filtrate was

concentrated under reduced pressure and the residue was purified by flash chromatography (hexane:Et₂O, 1:1) to afford amine **9** (816 mg, 57%) as a white solid: mp 98–99 °C; $[\alpha]_{\text{D}}^{20}$ -46.6 (c 1.28, CHCl₃); Rf 0.15 (hexane:Et₂O, 1:2); IR (thin film) 3666, 3642, 2983, 2928, 1453, 1375, 1248, 1214, 1139, 1053, 817, 748, 701 cm⁻¹; ¹H NMR δ 1.33 (3H, s), 1.55 (3H, s), 2.93 (1H, dd, *J* = 13.0, 9.7 Hz), 3.13 (1H, ddd, *J* = 9.6, 4.6, 1.4 Hz), 3.51 (1H, dd, *J* = 13.0, 4.6 Hz), 3.57 (1H, dd, *J* = 12.8, 2.1 Hz), 3.74 (1H, dd, *J* = 12.8, 4.9 Hz), 3.91 (1H, d, *J* = 12.3 Hz), 3.94–3.96 (1H, m), 4.10 (1H, d, *J* = 12.3 Hz), 4.18 (1H, dd, *J* = 7.2, 1.6 Hz), 7.30–7.52 (8H, m), 7.65 (1H, s), 7.79–7.85 (3H, m); ¹³C NMR δ 24.8 (CH₃), 26.7 (CH₃), 37.5 (CH₂), 50.7 (CH₂), 56.6 (CH), 60.6 (CH₂), 76.4 (CH), 77.8 (CH), 107.6 (C), 125.6 (CH), 126.3 (CH), 127.4 (CH), 127.5 (CH), 127.6 (CH), 127.7 (CH), 127.8 (CH), 128.4 (CH), 128.7 (CH), 128.7 (CH), 132.2 (C), 133.6 (C), 136.1 (C), 138.2 (C); MS (ESI) *m/z* (relative intensity) 392 ([M+H]⁺, 100), 393 (27), 394 (5); HRMS (ESI) calcd for C₂₅H₂₉NO₃ [M+H]⁺ 392.2220, found 392.2214.

Amine 10 (R=p-Me-benzyl). To a stirred solution of a 0.5M THF solution of *p*-methylbenzylmagnesium bromide (7.0 mL, 3.33 mmol) was added imine **6** (52.7 mg, 0.211 mmol) in dry THF (2 mL) dropwise at -20 °C under N₂. After the addition, the mixture was allowed to rise to room temperature and stirred for a further 17 h. The mixture was quenched with saturated NH₄Cl solution and the aqueous phase was extracted with EtOAc (3 × 20 mL). The combined organic extracts were dried over anhydrous MgSO₄, and filtered. The filtrate was concentrated under reduced pressure and the residue was purified by flash chromatography (hexane:Et₂O, 1:1) to afford amine **10** (27.3 mg, 50%) as a colourless oil: $[\alpha]_{\text{D}}^{20}$ -33.0 (c 1.13, CHCl₃); Rf 0.18 (hexane:Et₂O, 1:2); IR (thin film) 3415, 3335, 2984, 2926, 1701, 1513, 1456, 1375, 1214, 1046, 808, 746 cm⁻¹; ¹H NMR δ 1.31 (3H, s), 1.51 (3H, s), 2.34 (3H, s), 2.70 (1H, dd, *J* = 13.1, 9.8 Hz), 2.97 (1H, ddd, *J* = 9.7, 4.6, 1.6 Hz), 3.30 (1H, dd, *J* = 13.1, 4.6 Hz), 3.53 (1H, dd, *J* = 12.8, 2.1 Hz), 3.70 (1H, dd, *J* = 12.8, 4.8 Hz), 3.85 (1H, d, *J* = 12.3 Hz), 3.94–3.97 (1H, m), 4.05 (1H, d, *J* = 12.3 Hz), 4.14 (1H, dd, *J* = 7.2, 1.6 Hz), 7.06 (2H, d, *J* = 8.0 Hz), 7.12 (2H, d, *J* = 7.8 Hz), 7.27–7.35 (5H, m); ¹³C NMR δ 21.1 (CH₃), 24.8 (CH₃), 26.7 (CH₃), 36.9 (CH₂), 50.6 (CH₂), 56.7 (CH), 60.6 (CH₂), 76.4 (CH), 77.8 (CH), 107.5 (C), 127.6 (CH), 128.7 (CH), 128.7 (CH), 129.2 (CH), 129.4 (CH), 135.5 (C), 136.1 (C), 138.2 (C); MS (ESI) *m/z* (relative intensity) 356 ([M+H]⁺, 100), 357 (25), 358 (4); HRMS (ESI) calcd for C₂₂H₂₉NO₃ [M+H]⁺ 356.2220, found 356.2210.

Amine 11 (R=p-OMe-benzyl). To a stirred solution of a 0.5M THF solution of *p*-methoxybenzylmagnesium chloride (5.0 mL, 5.01 mmol) was added imine **6** (53.5 mg, 0.214 mmol) in dry THF (1 mL) dropwise at -20 °C under N₂. After the addition, the mixture was allowed to rise to room temperature and stirred for a further 17 h. The mixture was quenched with saturated NH₄Cl solution and the aqueous phase was extracted with EtOAc (3 × 20 mL). The combined organic extracts were dried over anhydrous MgSO₄, and filtered. The filtrate was

concentrated under reduced pressure and the residue was purified by flash chromatography (hexane:Et₂O, 1:1) to afford amine **11** (21.1 mg, 26%) as a colourless oil: $[\alpha]_{\text{D}}^{20}$ -35.9 (c 3.17, CHCl₃); R_f 0.13 (hexane:Et₂O, 1:2); IR (thin film) 3312, 2985, 2929, 1612, 1512, 1457, 1247, 1037, 747 cm⁻¹; ¹H NMR δ 1.32 (3H, s), 1.51 (3H, s), 2.69 (1H, dd, *J* = 13.2, 9.7 Hz), 2.95 (1H, ddd, *J* = 9.6, 4.6, 1.4 Hz), 3.26 (1H, dd, *J* = 13.2, 4.6 Hz), 3.54 (1H, dd, *J* = 12.8, 2.1 Hz), 3.70 (1H, dd, *J* = 12.8, 4.8 Hz), 3.79 (3H, s), 3.84 (1H, d, *J* = 12.3 Hz), 3.94–3.98 (1H, m), 4.04 (1H, d, *J* = 12.3 Hz), 4.14 (1H, dd, *J* = 7.2, 1.5 Hz), 6.85 (2H, d, *J* = 8.6 Hz), 7.09 (2H, d, *J* = 8.5 Hz), 7.28–7.36 (5H, m); ¹³C NMR δ 24.8 (CH₃), 26.7 (CH₃), 36.4 (CH₂), 50.6 (CH₂), 55.2 (CH₃), 56.6 (CH), 60.6 (CH₂), 76.3 (CH), 77.8 (CH), 107.5 (C), 114.1 (CH), 127.5 (CH), 128.6 (CH), 128.7 (CH), 130.2 (CH), 130.5 (C), 138.2 (C), 158.2 (C); MS (ESI) *m/z* (relative intensity) 372 ([M+H]⁺, 100), 373 (25), 374 (5); HRMS (ESI) calcd for C₂₂H₂₉NO₄ [M+H]⁺ 372.2169, found 372.2173.

Amine 12 (R=*p*-Cl-benzyl). To a stirred solution of a 0.5M THF solution of *p*-chlorobenzyl magnesium bromide (4.2 mL, 2.08 mmol) was added imine **6** (52 mg, 0.206 mmol) in dry THF (4 mL) dropwise at -20 °C under N₂. After the addition, the mixture was allowed to rise to room temperature and stirred for a further 24 h. The mixture was quenched with saturated NH₄Cl solution and the aqueous phase was extracted with EtOAc (3 × 20 mL). The combined organic extracts were dried over anhydrous MgSO₄, and filtered. The filtrate was concentrated under reduced pressure and the residue was purified by flash chromatography (hexane:Et₂O, 1:1) to afford amine **12** (35.8 mg, 46%) as a colourless oil: $[\alpha]_{\text{D}}^{20}$ -33.8 (c 2.59, CHCl₃); R_f 0.13 (hexane:Et₂O, 1:2); IR (thin film) 3316, 3028, 2983, 2927, 1491, 1452, 1376, 1247, 1214, 1087, 1051, 813 cm⁻¹; ¹H NMR δ 1.29 (3H, s), 1.49 (3H, s), 2.71 (1H, dd, *J* = 13.2, 9.8 Hz), 2.96 (1H, ddd, *J* = 9.6, 4.6, 1.5 Hz), 3.28 (1H, dd, *J* = 13.2, 4.6 Hz), 3.53 (1H, dd, *J* = 12.8, 2.1 Hz), 3.71 (1H, dd, *J* = 12.8, 4.9 Hz), 3.84 (1H, d, *J* = 12.3 Hz), 3.94–3.98 (1H, m), 4.02–4.07 (2H, m), 7.09 (2H, d, *J* = 8.3 Hz), 7.25–7.37 (7H, m); ¹³C NMR δ 24.7 (CH₃), 26.7 (CH₃), 36.7 (CH₂), 50.6 (CH₂), 56.5 (CH), 60.6 (CH₂), 76.3 (CH), 77.7 (CH), 107.7 (C), 127.7 (CH), 128.6 (CH), 128.8 (CH), 128.9 (CH), 130.6 (CH), 132.4 (C), 137.1 (C), 138.0 (C); MS (ESI) *m/z* (relative intensity) 376 ([M+H]⁺, 100), 377 (25), 378 (36), 379 (8), 380 (2); HRMS (ESI) calcd for C₂₁H₂₆NO₃Cl [M+H]⁺ 376.1674, found 376.1680.

Amine 13 (R=benzyl). To a solution of amine **7** (1.37 g, 4.00 mmol) in CH₂Cl₂ (53 mL) and then triethylamine (2.4 mL, 17.6 mmol) and methanesulfonyl chloride (0.68 mL, 8.81 mmol) were added under N₂ at 0 °C. The reaction mixture was stirred for 1 h and quenched with saturated NaHCO₃ solution. The aqueous phase was extracted with Et₂O (3 × 30 mL). The combined organic extracts were washed with brine, dried over anhydrous MgSO₄, and filtered. The filtrate was concentrated under reduced pressure and the residue was purified by flash chromatography (hexane:Et₂O, 1:1) to afford amine **13** (1.06 g, 82%) as a colourless oil: $[\alpha]_{\text{D}}^{20}$ -156.4 (c 1.94, CHCl₃); R_f 0.23

(hexane:Et₂O, 6:1); IR (thin film) 3027, 2982, 2932, 2787, 1451, 1373, 1210, 1133, 1102, 1033, 739, 700 cm⁻¹; ¹H NMR δ 1.42 (3H, s), 1.73 (3H, s), 2.08 (1H, dd, *J* = 11.2, 4.7 Hz), 2.41 (1H, dt, *J* = 10.1, 4.0 Hz), 3.01 (1H, dd, *J* = 13.2, 3.6 Hz), 3.14–3.22 (2H, m), 3.27 (1H, d, *J* = 13.5 Hz), 4.28 (1H, d, *J* = 13.5 Hz), 4.45 (1H, dd, *J* = 6.4, 4.5 Hz), 4.57 (1H, dd, *J* = 6.4, 4.8 Hz), 7.28–7.46 (10H, m); ¹³C NMR δ 25.8 (CH₃), 26.5 (CH₃), 33.3 (CH₂), 57.1 (CH₂), 59.9 (CH₂), 70.2 (CH), 77.5 (CH), 80.4 (CH), 111.0 (C), 125.9 (CH), 126.8 (CH), 128.2 (CH), 128.5 (CH), 129.5 (CH), 138.6 (C), 139.6 (C); MS (ESI) *m/z* (relative intensity) 324 ([M+H]⁺, 100), 325 (20), 326 (3); HRMS (ESI) calcd for C₂₁H₂₅NO₂ [M+H]⁺ 324.1958, found 324.1962.

Amine 14 (R=biphenylmethyl). To a solution of amine **8** (1.24 g, 2.98 mmol) in CH₂Cl₂ (40 mL) and then triethylamine (1.8 mL, 13.1 mmol) and methanesulfonyl chloride (0.51 mL, 6.55 mmol) were added under N₂ at 0 °C. The reaction mixture was stirred for 1 h and quenched with saturated NaHCO₃ solution. The aqueous phase was extracted with Et₂O (3 × 30 mL). The combined organic extracts were washed with brine, dried over anhydrous MgSO₄, and filtered. The filtrate was concentrated under reduced pressure and the residue was purified by flash chromatography (hexane:Et₂O, 1:1) to afford amine **14** (1.06 g, 88%) as a white solid: mp 120–121 °C; $[\alpha]_{\text{D}}^{20}$ -153.6 (c 1.30, CHCl₃); R_f 0.20 (hexane:Et₂O, 6:1); IR (thin film) 3659, 3471, 2943, 2767, 1439, 1375, 1211, 746 cm⁻¹; ¹H NMR δ 1.38 (3H, s), 1.68 (3H, s), 2.06 (1H, dd, *J* = 11.1, 4.7 Hz), 2.40 (1H, dt, *J* = 10.2, 4.0 Hz), 3.00 (1H, dd, *J* = 13.2, 3.5 Hz), 3.12 (1H, d, *J* = 11.2 Hz), 3.18 (1H, dd, *J* = 13.0, 10.5 Hz), 3.24 (1H, d, *J* = 13.5 Hz), 4.25 (1H, d, *J* = 13.5 Hz), 4.44–4.47 (1H, m), 4.54–4.57 (1H, m), 7.27–7.64 (14H, m); ¹³C NMR δ 25.9 (CH₃), 26.6 (CH₃), 33.1 (CH₂), 57.2 (CH₂), 59.9 (CH₂), 70.2 (CH), 77.6 (CH), 80.5 (CH), 111.2 (C), 126.9 (CH), 127.0 (CH), 127.1 (CH), 128.3 (CH), 128.6 (CH), 128.7 (CH), 130.0 (CH), 138.8 (C), 138.9 (C), 141.1 (C); MS (ESI) *m/z* (relative intensity) 400 ([M+H]⁺, 100), 401 (32), 402 (7); HRMS (ESI) calcd for C₂₇H₂₉NO₂ [M+H]⁺ 400.2271, found 400.2271.

Amine 15 (R=2-naphthylmethyl). To a solution of amine **9** (745 mg, 1.90 mmol) in CH₂Cl₂ (25 mL) and then triethylamine (1.16 mL, 8.37 mmol) and methanesulfonyl chloride (0.32 mL, 4.19 mmol) were added under N₂ at 0 °C. The reaction mixture was stirred at 0 °C for 1 h and quenched with saturated NaHCO₃ solution. The aqueous phase was extracted with Et₂O (3 × 30 mL). The combined organic extracts were washed with brine, dried over anhydrous MgSO₄, and filtered. The filtrate was concentrated under reduced pressure and the residue was purified by flash chromatography (hexane:Et₂O, 12:1) to afford amine **15** (695 mg, 98%) as a colourless oil; $[\alpha]_{\text{D}}^{20}$ -153.5 (c 2.99, CHCl₃); R_f 0.33 (hexane:Et₂O, 6:1); IR (thin film) 3054, 2980, 2932, 2787, 1601, 1449, 1372, 1271, 1209, 1131, 1093, 859, 748 cm⁻¹; ¹H NMR δ 1.43 (3H, s), 1.78 (3H, s), 2.08 (1H, dd, *J* = 11.2, 4.7 Hz), 2.49 (1H, dt, *J* = 10.2, 4.0 Hz), 3.16–3.20 (2H, m), 3.29 (1H, d, *J* = 13.5 Hz), 3.36 (1H, dd, *J* = 13.2, 10.2 Hz), 4.33 (1H, d, *J* = 13.5 Hz), 4.44 (1H, dd, *J* = 6.3, 4.5 Hz),

4.56 (1H, dd, $J = 6.4, 4.8$ Hz), 7.34–7.61 (8H, m), 7.87–7.92 (4H, m); ^{13}C NMR δ 25.8 (CH₃), 26.5 (CH₃), 33.5 (CH₂), 57.1 (CH₂), 59.9 (CH₂), 70.2 (CH), 77.5 (CH), 80.4 (CH), 111.0 (C), 125.2 (CH), 125.8 (CH), 126.8 (CH), 127.5 (CH), 127.6 (CH), 127.7 (CH), 127.7 (CH), 128.2 (CH), 128.2 (CH), 128.5 (CH), 132.0 (C), 133.5 (C), 137.2 (C), 138.7 (C); MS (ESI) m/z (relative intensity) 374 ([M+H]⁺, 100), 375 (94), 376 (5); HRMS (ESI) calcd for C₂₅H₂₇NO₂ [M+H]⁺ 374.2115, found 274.2121.

Amine 16 (R=*p*-Me-benzyl). To a solution of amine **10** (17.7 mg, 0.05 mmol) in CH₂Cl₂ (0.7 mL) and then triethylamine (0.03 mL, 0.22 mmol) and methanesulfonyl chloride (0.0085 mL, 0.11 mmol) were added under N₂ at 0 °C. The reaction mixture was stirred at 0 °C for 1.5 h and quenched with saturated NaHCO₃ solution. The aqueous phase was extracted with Et₂O (3 × 30 mL). The combined organic extracts were washed with brine, dried over anhydrous MgSO₄, and filtered. The filtrate was concentrated under reduced pressure and the residue was purified by flash chromatography (hexane:Et₂O, 12:1) to afford amine **16** (14.3 mg, 85%) as a colourless oil: $[\alpha]_{\text{D}}^{20}$ -149.3 (c 1.79, CHCl₃); R_f 0.27 (hexane:Et₂O, 6:1); IR (thin film) 3676, 3651, 3629, 3211, 3022, 2983, 2932, 2863, 2787, 1514, 1451, 1372, 1209, 942 cm⁻¹; ^1H NMR δ 1.35 (3H, s), 1.65 (3H, s), 2.02 (1H, dd, $J = 11.2, 4.8$ Hz), 2.31–2.36 (4H, m), 2.92 (1H, dd, $J = 13.2, 3.7$ Hz), 3.06–3.12 (2H, m), 3.20 (1H, d, $J = 13.5$ Hz), 4.22 (1H, d, $J = 13.5$ Hz), 4.41 (1H, dd, $J = 6.4, 4.5$ Hz), 4.53 (1H, dd, $J = 6.4, 4.8$ Hz), 7.13–7.40 (9H, m); ^{13}C NMR δ 21.1 (CH₃), 25.90 (CH₃), 26.5 (CH₃), 32.9 (CH₂), 57.2 (CH₂), 60.0 (CH₂), 70.4 (CH), 77.6 (CH), 80.5 (CH), 111.1 (C), 126.8 (CH), 128.2 (CH), 128.6 (CH), 129.0 (CH), 129.4 (CH), 135.4 (C), 136.6 (C), 138.8 (C); MS (ESI) m/z (relative intensity) 338 ([M+H]⁺, 100), 339 (26), 340 (4); HRMS (ESI) calcd for C₂₂H₂₇NO₂ [M+H]⁺ 338.2115, found 338.2118.

Amine 17 (R=*p*-OMe-benzyl). To a solution of amine **11** (13.0 mg, 0.0349 mmol) in CH₂Cl₂ (0.5 mL) and then triethylamine (0.02 mL, 0.153 mmol) and methanesulfonyl chloride (0.0059 mL, 0.0767 mmol) were added under N₂ at 0 °C. The reaction mixture was stirred at 0 °C for 1 h and quenched with saturated NaHCO₃ solution. The aqueous phase was extracted with Et₂O (3 × 30 mL). The combined organic extracts were washed with brine, dried over anhydrous MgSO₄, and filtered. The filtrate was concentrated under reduced pressure and the residue was purified by flash chromatography (hexane:Et₂O, 12:1) to afford amine **17** (10.3 mg, 83%) as a colourless oil: $[\alpha]_{\text{D}}^{20}$ -145.7 (c 2.58, CHCl₃); R_f 0.13 (hexane:Et₂O, 6:1); IR (thin film) 3027, 2983, 2933, 2830, 2787, 1611, 1512, 1452, 1372, 1244, 1036, 835 cm⁻¹; ^1H NMR δ 1.34 (3H, s), 1.64 (3H, s), 2.02 (1H, dd, $J = 11.2, 4.8$ Hz), 2.30 (1H, dt, $J = 10.3, 4.0$ Hz), 2.89 (1H, dd, $J = 13.3, 3.7$ Hz), 3.02–3.09 (2H, m), 3.20 (1H, d, $J = 13.6$ Hz), 3.81 (3H, s), 4.21 (1H, d, $J = 13.6$ Hz), 4.39 (1H, dd, $J = 6.4, 4.5$ Hz), 4.52 (1H, dd, $J = 6.4, 4.7$ Hz), 6.87 (2H, d, $J = 8.6$ Hz), 7.24–7.37 (7H, m); ^{13}C NMR δ 25.9 (CH₃), 26.5 (CH₃), 32.4 (CH₂), 55.2

(CH₃), 57.1 (CH₂), 60.0 (CH₂), 70.4 (CH), 77.5 (CH), 80.5 (CH), 111.0 (C), 113.6 (CH), 126.8 (CH), 128.2 (CH), 128.6 (CH), 130.4 (CH), 131.6 (C), 138.7 (C), 157.9 (C); MS (ESI) m/z (relative intensity) 354 ([M+H]⁺, 100), 355 (22), 356 (4); HRMS (ESI) calcd for C₂₂H₂₇NO₃ [M+H]⁺ 342.2064, found 342.2058.

Amine 18 (R=*p*-Cl-benzyl). To a solution of amine **12** (32.7 mg, 0.0869 mmol) in CH₂Cl₂ (1.1 mL) and then triethylamine (0.05 mL, 0.382 mmol) and methanesulfonyl chloride (0.015 mL, 0.191 mmol) were added under N₂ at 0 °C. The reaction mixture was stirred at 0 °C for 1 h and quenched with saturated NaHCO₃ solution. The aqueous phase was extracted with Et₂O (3 × 30 mL). The combined organic extracts were washed with brine, dried over anhydrous MgSO₄, and filtered. The filtrate was concentrated under reduced pressure and the residue was purified by flash chromatography (hexane:Et₂O, 12:1) to afford amine **18** (28.1 mg, 90%) as a colourless oil; $[\alpha]_{\text{D}}^{20}$ -159.2 (c 1.82, CHCl₃); R_f 0.17 (hexane:Et₂O, 12:1); IR (thin film) 3027, 2980, 2932, 2787, 1491, 1451, 1373, 1210, 1133, 1089, 862, 743 cm⁻¹; ^1H NMR δ 1.32 (3H, s), 1.61 (3H, s), 2.03 (1H, dd, $J = 11.2, 4.8$ Hz), 2.29 (1H, dt, $J = 10.4, 4.1$ Hz), 2.89 (1H, dd, $J = 13.2, 3.8$ Hz), 3.01–3.08 (2H, m), 3.21 (1H, d, $J = 13.6$ Hz), 4.16 (1H, d, $J = 13.6$ Hz), 4.33 (1H, dd, $J = 6.4, 4.6$ Hz), 4.51 (1H, dd, $J = 6.4, 4.7$ Hz), 7.24–7.37 (9H, m); ^{13}C NMR δ 25.8 (CH₃), 26.5 (CH₃), 32.9 (CH₂), 57.1 (CH₂), 59.9 (CH₂), 70.1 (CH), 77.5 (CH), 80.3 (CH), 111.2 (C), 126.9 (CH), 128.3 (CH), 128.4 (CH), 128.6 (CH), 130.9 (CH), 131.8 (C), 138.0 (C), 138.6 (C); MS (ESI) m/z (relative intensity) 358 ([M+H]⁺, 100), 359 (24), 360 (34), 361 (9); HRMS (ESI) calcd for C₂₁H₂₄NO₃Cl [M+H]⁺ 358.1568, found 358.1571.

Amine 19 (R=benzyl). To a solution of amine **13** (444 mg, 1.38 mmol) in *t*-BuOH (23 mL) and water (4.5 mL) was added 10% Pd-on-charcoal (147 mg, 0.138 mmol) The mixture was activated with an atmosphere of H₂ (balloon) by three times followed by stirring under the same H₂ atmosphere at room temperature for another 48 h. The mixture was filtered and washed with EtOAc. The filtrate was concentrated under reduced pressure and the residue was purified by flash chromatography (CHCl₃:MeOH, 20:1) to afford amine **19** (293 mg, 91%) as a colourless oil: $[\alpha]_{\text{D}}^{20}$ -93.4 (c 1.75, CHCl₃); R_f 0.40 (CHCl₃:MeOH, 20:1); ^1H NMR δ 1.32 (3H, s), 1.51 (3H, s), 1.93 (1H, br s), 2.60 (1H, dd, $J = 13.3, 4$ Hz), 2.81–2.89 (2H, m), 2.95–3.01 (1H, m), 3.06 (1H, d, $J = 13.3$ Hz), 4.40 (1H, dd, $J = 5.5, 3.5$ Hz), 4.62 (1H, dd, $J = 5.5, 4.0$ Hz), 7.18–7.32 (5H, m); ^{13}C NMR δ 23.9 (CH₃), 25.8 (CH₃), 34.7 (CH₂), 53.1 (CH₂), 65.5 (CH), 81.1 (CH), 81.8 (CH), 110.3 (C), 126.0 (CH), 128.2 (CH), 129.0 (CH), 139.5 (C); MS (ESI) m/z (relative intensity) 234 ([M+H]⁺, 100), 235 (15), 236 (2); HRMS (ESI) calcd for C₁₄H₁₉NO₂ [M+H]⁺ 234.1489, found 234.1489.

Amine 20 (R=biphenylmethyl). To a solution of amine **14** (367 mg, 0.917 mmol) in *t*-BuOH (30 mL) and water (6 mL) was added 10% Pd-on-charcoal (97.6 mg, 0.0917 mmol) The

mixture was activated with an atmosphere of H₂ (balloon) by three times followed by stirring under the same H₂ atmosphere at room temperature for another 72 h. The mixture was filtered and washed with EtOAc. The filtrate was concentrated under reduced pressure and the residue was purified by flash chromatography (CHCl₃:MeOH, 20:1) to afford amine **20** (250 mg, 88%) as a white solid: mp 89–90 °C; [α]_D²⁰ –92.9 (c 1.10, CHCl₃); R_f 0.33 (CHCl₃:MeOH, 20:1); IR (thin film) 3671, 3648, 3027, 2982, 2927, 2860, 1488, 1376, 1269, 1207, 1080, 1036, 853, 762 cm⁻¹; ¹H NMR δ 1.34 (3H, s), 1.54 (3H, s), 2.06 (1H, br s), 2.62 (1H, dd, *J* = 13.4, 4.0 Hz), 2.86–2.94 (2H, m), 3.00–3.06 (1H, m), 3.09 (1H, d, *J* = 13.3 Hz), 4.47 (1H, dd, *J* = 5.4, 3.4 Hz), 4.66 (1H, dd, *J* = 5.5, 4.0 Hz), 7.31–7.53 (9H, m); ¹³C NMR δ 24.0 (CH₃), 25.9 (CH₃), 34.4 (CH₂), 53.3 (CH₂), 65.6 (CH), 81.3 (CH), 82.0 (CH), 110.4 (C), 127.0 (CH), 127.0 (CH), 127.1 (CH), 128.7 (CH), 129.5 (CH), 138.8 (C), 139.1 (C), 141.1 (C); MS (ESI) *m/z* (relative intensity) 310 ([M+H]⁺, 100), 311 (23), 312 (3); HRMS (ESI) calcd for C₂₀H₂₃NO₂ [M+H]⁺ 310.1802, found 310.1801.

Amine 21 (R=2-naphthylmethyl). To a solution of amine **15** (41.4 mg, 0.111 mmol) in *t*-BuOH (1.6 mL) and water (0.4 mL) was added 10% Pd-on-charcoal (11.8 mg, 0.0111 mmol) The mixture was activated with an atmosphere of H₂ (balloon) by three times followed by stirring under the same H₂ atmosphere at room temperature for another 48 h. The mixture was filtered and washed with EtOAc. The filtrate was concentrated under reduced pressure and the residue was purified by flash chromatography (CHCl₃:MeOH, 20:1) to afford amine **21** (30.5 mg, 97%) as a colourless oil: [α]_D²⁰ –102.3 (c 1.03, CHCl₃); R_f 0.33 (CHCl₃:MeOH, 20:1); IR (thin film) 3051, 2981, 2929, 2860, 1441, 1375, 1269, 1206, 1162, 1036, 985, 858, 819, 749 cm⁻¹; ¹H NMR δ 1.33 (3H, s), 1.55 (3H, s), 2.26 (1H, br s), 2.61 (1H, dd, *J* = 13.3, 3.8 Hz), 2.92–2.96 (1H, m), 3.02–3.18 (3H, m), 4.42–4.45 (1H, m), 4.63–4.65 (1H, m), 7.40–7.79 (7H, m); ¹³C NMR δ 24.0 (CH₃), 25.9 (CH₃), 34.9 (CH₂), 53.2 (CH₂), 65.3 (CH), 81.2 (CH), 81.9 (CH), 110.4 (C), 125.3 (CH), 125.9 (CH), 127.4 (CH), 127.5 (CH), 127.6 (CH), 127.7 (CH), 127.9 (CH), 132.2 (C), 133.6 (C), 137.1 (C); MS (ESI) *m/z* (relative intensity) 284 ([M+H]⁺, 100), 285 (23), 286 (3); HRMS (ESI) calcd for C₁₈H₂₁NO₂ [M+H]⁺ 284.1645, found 284.1641.

Amine 22 (R=*p*-Me-benzyl). To a solution of amine **16** (46.9 mg, 0.139 mmol) in *t*-BuOH (3.3 mL) and water (0.7 mL) was added 10% Pd-on-charcoal (148 mg, 0.139 mmol) The mixture was activated with an atmosphere of H₂ (balloon) by three times followed by stirring under the same H₂ atmosphere at room temperature for another 24 h. The mixture was filtered and washed with EtOAc. The filtrate was concentrated under reduced pressure and the residue was purified by flash chromatography (CHCl₃:MeOH, 20:1) to afford amine **22** (33.5 mg, 97%) as a colourless oil: [α]_D²⁰ –93.6 (c 1.51, CHCl₃); R_f 0.36 (CHCl₃:MeOH, 20:1); IR (thin film) 3671, 3270, 2982, 2925, 2862, 1647, 1515, 1450, 1376, 1269, 1208, 1163, 1081, 1036, 818 cm⁻¹; ¹H NMR δ 1.31 (3H, s), 1.51 (3H, s), 2.16 (1H,

br s), 2.31 (3H, s), 2.58 (1H, dd, *J* = 13.3, 4.0 Hz), 2.78–2.85 (2H, m), 2.91–2.97 (1H, m), 3.06 (1H, d, *J* = 13.3 Hz), 4.41 (1H, dd, *J* = 5.5, 3.3 Hz), 4.62 (1H, dd, *J* = 5.5, 4.1 Hz), 7.10 (2H, d, *J* = 7.8 Hz), 7.19 (2H, d, *J* = 8.0 Hz); ¹³C NMR δ 21.0 (CH₃), 23.9 (CH₃), 25.9 (CH₃), 34.2 (CH₂), 53.1 (CH₂), 65.7 (CH), 81.2 (CH), 81.9 (CH), 110.3 (C), 128.9 (CH), 129.0 (CH), 135.5 (C), 136.4 (C); MS (ESI) *m/z* (relative intensity) 248 ([M+H]⁺, 100), 249 (18), 250 (2); HRMS (ESI) calcd for C₁₅H₂₁NO₂ [M+H]⁺ 248.1645, found 248.1647.

Amine 23 (R=*p*-OMe-benzyl). To a solution of amine **17** (41.5 mg, 0.118 mmol) in *t*-BuOH (1.7 mL) and water (0.3 mL) was added 10% Pd-on-charcoal (12.5 mg, 0.0118 mmol) The mixture was activated with an atmosphere of H₂ (balloon) by three times followed by stirring under the same H₂ atmosphere at room temperature for another 12 h. The mixture was filtered and washed with EtOAc. The filtrate was concentrated under reduced pressure and the residue was purified by flash chromatography (CHCl₃:MeOH, 20:1) to afford amine **23** (27.3 mg, 88%) as a pale yellow oil: [α]_D²⁰ –89.5 (c 1.06, CHCl₃); R_f 0.27 (CHCl₃:MeOH, 20:1); IR (thin film) 2983, 2929, 2831, 1649, 1513, 1459, 1246, 1036, 833 cm⁻¹; ¹H NMR δ 1.31 (3H, s), 1.50 (3H, s), 2.13 (1H, br s), 2.59 (1H, dd, *J* = 13.3, 3.9 Hz), 2.76–2.83 (2H, m), 2.88–2.95 (1H, m), 3.06 (1H, d, *J* = 13.3 Hz), 3.78 (3H, s), 4.41 (1H, dd, *J* = 5.4, 3.3 Hz), 4.62 (1H, dd, *J* = 5.4, 4.1 Hz), 6.83 (2H, d, *J* = 7.8 Hz), 7.21 (2H, d, *J* = 8.6 Hz); ¹³C NMR δ 24.0 (CH₃), 25.9 (CH₃), 33.8 (CH₂), 53.2 (CH₂), 55.2 (CH₃), 65.8 (CH), 81.2 (CH), 81.9 (CH), 110.4 (C), 113.8 (CH), 130.0 (CH), 131.6 (C), 158.0 (C); MS (ESI) *m/z* (relative intensity) 264 ([M+H]⁺, 100), 265 (17), 266 (2); HRMS (ESI) calcd for C₁₅H₂₁NO₃ [M+H]⁺ 264.1594, found 264.1600.

Amine 24 (R=*p*-Cl-benzyl). To a solution of amine **18** (30 mg, 0.0838 mmol) in dry CH₂Cl₂ (0.6 mL) was added chloroethylchloroformate (0.0135 mL, 0.126 mmol) at 0 °C under N₂. The solution was stirred at 0 °C for 13 h and the solvent was removed under reduced pressure. The residue was redissolved in MeOH (1 mL) and the mixture was then heated to reflux for 2 h. The reaction mixture was concentrated under reduced pressure and the crude residue was directly purified by flash chromatography (CHCl₃:MeOH, 20:1) to afford amine **24** (7.1 mg, 32%) as a colourless oil: [α]_D²⁰ –95.2 (c 0.36, CHCl₃); R_f 0.33 (CHCl₃:MeOH, 20:1); IR (thin film) 2982, 2929, 2845, 1491, 1376, 1270, 1207, 1165, 1080, 1036, 983, 856 cm⁻¹; ¹H NMR δ 1.31 (3H, s), 1.50 (3H, s), 1.83 (1H, br s), 2.60 (1H, dd, *J* = 13.4, 3.8 Hz), 2.77–2.86 (2H, m), 2.92–2.97 (1H, m), 3.07 (1H, d, *J* = 13.3 Hz), 4.39 (1H, dd, *J* = 5.2, 3.6 Hz), 4.64 (1H, dd, *J* = 5.2, 4.3 Hz), 7.20–7.25 (4H, m); ¹³C NMR δ 24.0 (CH₃), 25.9 (CH₃), 34.1 (CH₂), 53.2 (CH₂), 65.5 (CH), 81.1 (CH), 81.9 (CH), 110.5 (C), 128.5 (CH), 130.5 (CH), 132.0 (C), 138.0 (C); MS (ESI) *m/z* (relative intensity) 268 ([M+H]⁺, 100), 269 (16), 270 (30), 271 (6); HRMS (ESI) calcd for C₁₄H₁₈NO₃Cl [M+H]⁺ 268.1099, found 268.1105.

Dienol 30. To a solution of the anime **19** (9.3 mg, 0.04 mmol) and *o*-NO₂-benzoic acid (6.7 mg, 0.04 mmol) in a CHCl₃ (0.5 mL) was added dienal **28** (62.4 mg, 0.201 mmol) in CHCl₃ (1.5 mL) at room temperature and stirred at same temperature for 20 h until the disappearance of the starting material as shown on TLC. The reaction mixture was filtered through a thin pad of silica gel and the filtrate was concentrated under reduced pressure. The residue was redissolved in EtOH (2 mL) and NaBH₄ (6.3 mg, 0.168 mmol) was added to crude product at 0 °C for 1 h. The mixture was quenched with saturated NH₄Cl solution and the aqueous phase was extracted with EtOAc (3 × 10 mL). The combined organic extracts were dried over anhydrous MgSO₄, and filtered. The filtrate was concentrated under reduced pressure and the residue was purified by flash chromatography (hexane:EtOAc, 10:1) gave dienol **30** (6.4 mg, 11%) as a colourless oil: R_f 0.40 (hexane:EtOAc, 3:1); IR (thin film) 3357, 3028, 2928, 2857, 1464, 1367, 1252, 1105, 1037, 835, 773 cm⁻¹; ¹H NMR δ 0.02–0.03 (6H, m), 0.87 (9H, s), 1.35–1.50 (2H, m), 1.62–1.83 (5H, m), 1.99–2.07 (1H, m), 2.48–2.56 (1H, m), 4.08–4.09 (1H, m), 4.18–4.26 (2H, m), 5.58 (1H, d, *J* = 7.0 Hz), 5.59–5.94 (2H, m); ¹³C NMR (MeOD) δ –4.73 (CH₃), 18.9 (C), 23.9 (CH₂), 26.3 (CH₃), 34.9 (CH₂), 35.2 (CH), 41.1 (CH₂), 42.4 (CH), 63.8 (CH₂), 68.5 (CH), 121.8 (CH), 125.2 (CH), 133.8 (CH), 142.6 (C); MS (EI) *m/z* (relative intensity) 294 ([M]⁺, 100); HRMS (EI) calcd for C₁₇H₃₀O₂Si [M]⁺ 294.2010, found 294.2009.

Dienol 33. To a solution of the anime **19** (6.8 mg, 0.029 mmol) and *o*-NO₂-benzoic acid (4.9 mg, 0.029 mmol) in a CHCl₃ (0.5 mL) was added dienal **31** (39.4 mg, 0.148 mmol) in CHCl₃ (1 mL) at room temperature and stirred at same temperature for 9 h until the disappearance of the starting material as shown on TLC. The reaction mixture was filtered through a thin pad of silica gel and the filtrate was concentrated under reduced pressure. The residue was redissolved in EtOH (1.5 mL) and NaBH₄ (6.3 mg, 0.168 mmol) was added to crude product at 0 °C for 1 h. The mixture was quenched with saturated NH₄Cl solution and the aqueous phase was extracted with EtOAc (3 × 10 mL). The combined organic extracts were dried over anhydrous MgSO₄, and filtered. The filtrate was concentrated under reduced pressure and the residue was purified by flash chromatography (hexane:EtOAc, 5:1) gave dienol **33** (5.9 mg, 16%) as a white solid: mp 61–62 °C; R_f 0.26 (hexane:EtOAc, 4:1); IR (thin film) 3284, 3025, 2983, 2918, 2857, 1437, 1374, 1257, 1206, 1164, 1049, 1001, 874, 713 cm⁻¹; ¹H NMR δ 1.38 (6H, s), 1.59–1.70 (3H, m), 1.85–1.92 (2H, m), 1.99–2.06 (2H, m), 2.43–2.51 (1H, m), 3.74 (2H, s), 4.17–4.26 (2H, m), 5.58–5.61 (1H, m), 5.93–5.95 (2H, m); ¹³C NMR δ 24.5 (CH₂), 27.4 (CH₃), 27.5 (CH₃), 36.1 (CH₂), 36.2 (CH), 40.5 (CH), 41.9 (CH₂), 64.1 (CH₂), 74.8 (CH₂), 80.5 (C), 109.4 (C), 121.4 (CH), 124.1 (CH), 132.9 (CH), 141.1 (C); MS (EI) *m/z* (relative intensity) 250 ([M]⁺, 100); HRMS (EI) calcd for C₁₅H₂₂O₃ [M]⁺ 250.1563, found 250.1563.

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Notes and references

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