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A convenient 5-*exo-dig* cyclization route to diastereomerically pure methyl (2*S*)-2-(1-benzyl-3-oxo-1,3-dihydro-2*H*-isoindol-2-yl)-3-methylbutanoate

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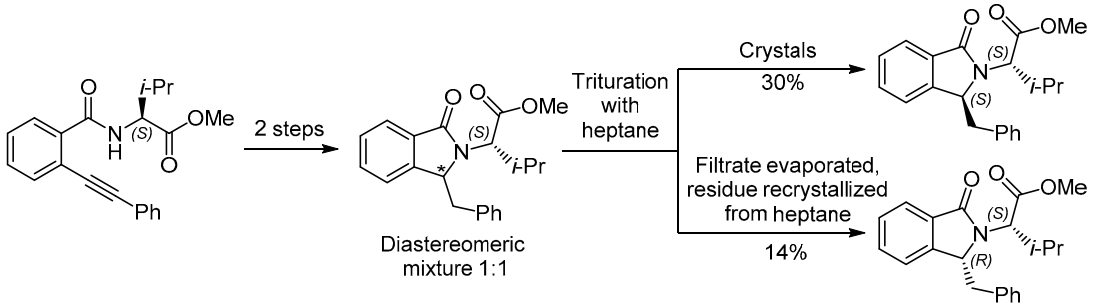


A robust method toward the synthesis of diastereomerically pure methyl (2*S*)-2-(1-benzyl-3-oxo-1,3-dihydro-2*H*-isoindol-2-yl)-3-methylbutanoate has been described. The key reactions in the synthesis are: HATU-mediated coupling, Pd-catalyzed Sonogashira coupling, base-mediated 5-*exo-dig* cyclization, and catalytic hydrogenation. The diastereomeric mixture is subjected to trituration with heptane to furnish both diastereomers in moderate yields. The relative stereochemistry was confirmed by the single crystal X-ray diffractometry. The key feature of the method is the simplicity of the diastereomeric separation.

Keywords: oxoisoindoline, cyclization, diastereoselectivity, enantioselectivity, Sonogashira coupling.

Isoindolin-1-one is a common moiety present in many natural products like nuevamine,[1] magallanesine,[2] staurosporine etc.[3] More specifically, 3-substituted isoindolin-1-ones are found in pharmacologically important synthetic drugs such as pazinaclone,[4] renin inhibitors,[5] antiarrhythmic agents,[6] and HIV reverse transcriptase inhibitor[7] (Fig. 1). Organic compounds possessing isoindolin-1-one moiety display wide range of biological activities such as antiviral,[8] antibacterial,[9] HIV-1 inhibiting,[10] sedative, and hypnotic.[11] Numerous scientific studies claim that some isoindolin-1-ones help in the treatment of cancer,[12] CNS diseases,[13] diabetes,[14] obesity, and hyperlipidemia.[15] Isoindolin-1-ones have also been employed as pivotal substrates in the variety of organic transformations[16–18] such as Diels–Alder reaction, asymmetric synthesis, etc. Due to the vast range of medicinal activities of isoindolin-1-ones, a variety of approaches have been developed for the synthesis of these significant motifs.[19–21] However, synthetic strategies toward the synthesis of asymmetric 3-substituted isoindolin-1-ones have been limited. Few notable mentions include (a) asymmetric Michael reaction of 3-substituted isoindolinones using quinine-derived phase-transfer catalyst[22] with moderate enantiomeric excess, (b) Pd-catalyzed hydrogenation of *N*-substituted 3-methyleneisoindolin-1-ones with poor diastereoselectivity,[23] (c) multicomponent reaction involving 2-formylbenzoic acid, chiral methylbenzylamine, and dimethyl phosphite, under solvent- and catalyst-free conditions, with good yield and high diastereoselectivity (95:5 *dr*),[24] (d) diastereoselective reductive alkylation approach to *N*-protected (*R*)-3-alkylisoindolin-1-ones using $BF_3{\cdot}OEt_2/Et_3SiH$,[25] (e) asymmetric alkylation of indolin-1-ones through the formation of unstabilized carbanion using LDA or NaHMDS.[26]

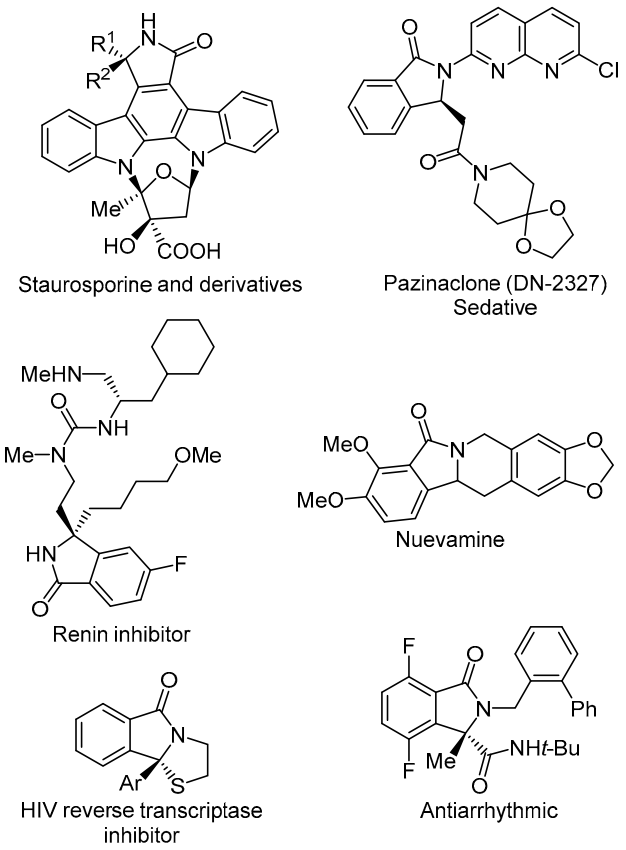


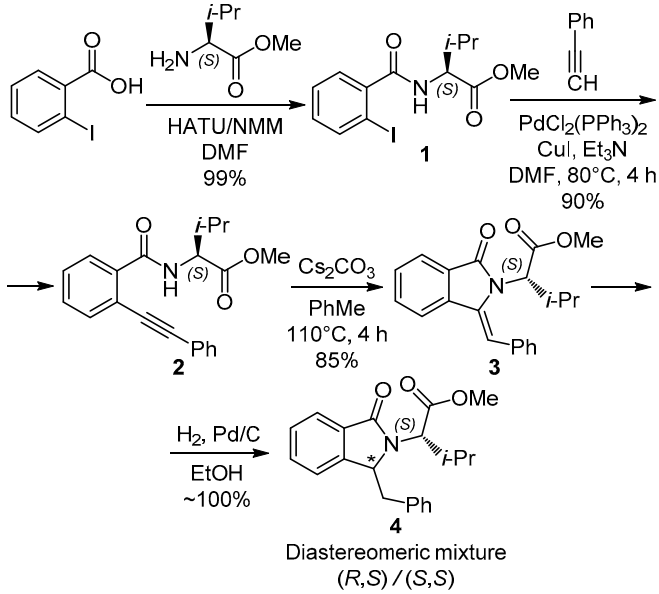
Figure 1. Substituted isoindolin-1-ones with biological activity.

In the past decade, the ability of L-amino acids to catalyze certain reactions has been explored, which has paved the way for asymmetric organocatalysis.[27–30] A careful study of isoindolin-1-one structure revealed that MeO-L-valine can be exploited to control the stereochemistry at position 3 of isoindolin-1-one. Herein, we report a facile method toward the synthesis of enantiomerically pure 3-substutited isoindolin-1-one *via* base-mediated 5-*exo-dig* cyclization and catalytic hydrogenation followed by trituration with heptane to furnish both diastereomers.

Our synthetic endeavors started with commercially available 2-iodobenzoic acid which was coupled with MeO-L-valine using HATU as a coupling reagent and NMM as a base to give iodoamide **1** in almost quantitative yield (Scheme 1). The Pd/Cu-catalyzed Sonogashira coupling reaction of iodoamide **1** with phenylacetylene gave amidoalkyne **2** in 90% yield. At this stage, we explored several options to cyclize amidoalkyne **2** into 3-alkylideneisoindolin-1-one **3** using Na_2CO_3,[31] *n*-BuLi/I_2/ICl,[32] $Pd(OAc)_2/PPh_3$,[33] and TBAF.[34] In most cases, we observed formation of trace amount of desired product **3** along with some impurities. However, with Na_2CO_3 moderate yields could be obtained when toluene is used as solvent (Table 1, entry 2).

Then, a systematic study of 5-*exo-dig* cyclization in the presence of several other bases was performed (Table 1). The use of Cs_2CO_3 as a versatile base is well documented in literature.[35] Using a combination of PhMe and Cs_2CO_3,

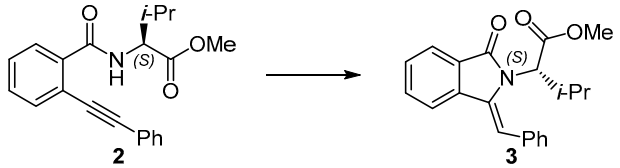
Scheme 1. Synthesis of diastereomeric mixture of methyl (2*S*)-2-(1-benzyl-3-oxo-1,3-dihydro-2*H*-isoindol-2-yl)-3-methylbutanoate (**4**)



we observed the formation of 3-alkylideneisoindolin-1-one **3** in 85% yield (Table 1, entry 8). The formation of isoindolin-1-one derivative **3** was unambiguously confirmed by ^{1}H NMR spectroscopy. Compound **3** was then subjected to Pd-catalyzed hydrogenation which provided the title compound **4** as 1:1 diastereomeric mixture (*R*,*S* and *S*,*S*) in quantitative yield (Scheme 1). The formation of 1:1 diastereomeric mixture was confirmed based on the ^{1}H NMR data.

In order to separate the diastereomers, we performed column chromatographic purification. In the end, it proved

Table 1. Optimization of the conditions in 5-*exo-dig* cyclization for the synthesis of compound **3***

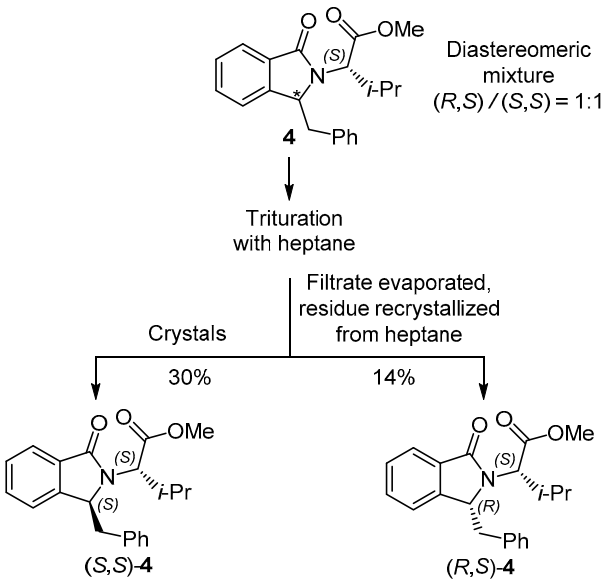


Entry	Base	Solvent	Isolated yield of compound **3**, %
1	Na_2CO_3	DMF	36
2	Na_2CO_3	PhMe	41
3	K_3PO_4	DMF	nr**
4	K_3PO_4	PhMe	nr
5	NaOH	DMF	nr
6	NaOH	PhMe	nr
7	Cs_2CO_3	DMF	54
8	Cs_2CO_3	PhMe	85
9	Cs_2CO_3	THF	25***

* Reaction conditions: compound **2** (1 equiv), base (1 equiv), solvent (5 ml), 110°C, 4 h.
** nr – no reaction.
*** Reaction conditions: compound **2** (1 equiv), base (1 equiv), solvent (5 ml), 60°C, 4 h.

unproductive, due to the close R_f of both isomers on TLC. Simple separation methods such as filtration, distillation, trituration, etc, are most sought-after techniques from the point of view of pharmaceutical industry. We then directed our attention toward the sticky nature of compound **4** and realized that trituration could be a method of choice in this case. For trituration, we screened a variety of single solvents and mixtures of solvents like Et_2O, hexane, pentane, heptane, EtOAc–hexane (1→10%), Et_2O–hexane, 1:1. The best result was obtained using single solvent, heptane. Diastereomeric mixture was taken in heptane and stirred at room temperature for 1 h resulting in a fine crystalline white powder of diastereomer (*S*,*S*)-**4** in 30% yield after filtration. The ^{1}H NMR confirmed the presence of single diastereomer (*S*,*S*)-**4** (*de* > 99%). Single X-ray crystal data was recorded in order to establish the relative stereochemistry and it was found to be *S*,*S* (Scheme 2, Fig. 2). The mother liquor was concentrated and recrystallized from heptane to obtain the other diastereomer (*R*,*S*)-**4** in 14% yield (*de* 75%). Unfortunately, crystals suitable for the X-ray analysis could not be obtained for diastereomer (*R*,*S*)-**4**, its structure therefore was confirmed by ^{1}H NMR spectroscopy (Scheme 2).

Scheme 2. Separation of diastereomers of methyl (2*S*)-2-(1-benzyl-3-oxo-1,3-dihydro-2*H*-isoindol-2-yl)-3-methylbutanoate (**4**) by trituration with heptane



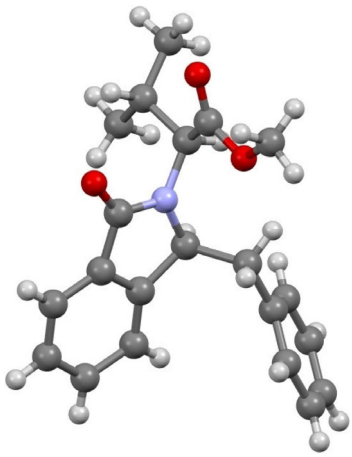


Figure 2. Crystal structure of compound (*S*,*S*)-**4**.

In summary, we have demonstrated an elegant 5-*exo*-*dig* cyclization strategy for the synthesis of both diastereomers of methyl (2*S*)-2-(1-benzyl-3-oxo-1,3-dihydro-2*H*-isoindol-2-yl)-3-methylbutanoate. Diastereomers were separated by a simple trituration process. The extension of the current methodology on other 3-substituted isoindolin-1-ones is being explored in our laboratory.

Experimental

The IR spectra were recorded on a PerkinElmer 683 B FT-IR spectrometer. ^{1}H and ^{13}C NMR spectra (400 and 100 MHz, respectively) were recorded on a Bruker Avance 400 MHz spectrometer in $CDCl_3$ with TMS as internal standard. HRMS were acquired on a VG-Autospec M-250 instrument with electrospray ionization. Optical rotations were measured using Na D line on a JASCO DIP-181 digital polarimeter. Column chromatographic separations were carried out on CDH silica gel (60–120 mesh).

Commercially available HATU, NMM, phenylacetylene, Cs_2CO_3, CuI, Pd/C (10 wt %), $PdCl_2(PPh_3)_2$ were used. Compound **1** was prepared using known procedure.[36]

Methyl (2*S*)-3-methyl-2-{[2-(phenylethynyl)benzoyl]-amino}butanoate (2). $PdCl_2(PPh_3)_2$ (0.05 g, 5 mol %) and Et_3N (0.5 g, 0.0053 mol) were added to a stirring solution of methyl (2-iodobenzoyl)-L-valinate (**1**) (1 g, 0.0026 mol) in DMF (5 ml) under N_2 atmosphere, and the reaction mixture was stirred for 10 min. This was followed by the addition of phenylacetylene (0.40 g, 0.0039 mol), and the reaction mass was heated to 80°C for 4 h. It was cooled to 25°C, and H_2O (5 ml) was added to the reaction mixture and extracted with EtOAc (20 ml). EtOAc layer was dried over Na_2SO_4 and concentrated to get crude product which was purified by silica gel column chromatography using EtOAc–*n*-hexane, 30%, as an eluent. Yield 835 mg (90%), thick oil. $[\alpha]_D^{25}$ +24.5 (*c* 0.6, $CHCl_3$). IR spectrum ($CHCl_3$), ν, cm^{-1}: 2200, 1740, 1670. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 0.96 (3H, d, *J* = 8.1, CH_3); 1.01 (3H, d, *J* = 8.2, CH_3); 2.24–2.29 (1H, m, C<u>H</u>$(CH_3)_2$); 3.72 (3H, s, OCH_3); 4.86 (1H, t, *J* = 4.4, CH); 7.39–7.41 (3H, m, H Ar); 7.40–7.50 (2H, m, H Ar); 7.61–7.65 (2H, m, H Ar); 7.66–7.68 (1H, m, H Ar); 8.00 (1H, br. s, NH); 8.11–8.13 (1H, m, H Ar). ^{13}C NMR spectrum, δ, ppm: 18.3; 19.0; 31.6; 52.1; 58.2; 87.4; 96.1; 120.0; 122.3; 128.4; 128.8; 129.1; 130.2; 130.8; 131.8; 134.0; 134.7; 166.0; 172.3. Found, *m*/*z*: 358.1435 $[M+Na]^+$. $C_{21}H_{21}NNaO_3$. Calculated, *m*/*z*: 358.1414.

Methyl (2*S*)-2-[(1*Z*)-1-benzylidene-3-oxo-1,3-dihydro-2*H*-isoindol-2-yl]-3-methylbutanoate (3). Cs_2CO_3 (0.795 g, 0.003 mol) was added to a stirring solution of methyl (2*S*)-3-methyl-2-{[2-(phenylethynyl)benzoyl]amino}butanoate (**2**) (1 g, 0.003 mol) in PhMe (5 ml), and the reaction mixture was heated to 110°C for 4 h. It was cooled to room temperature, and H_2O (5 ml) was added. The product was extracted with EtOAc (25 ml). Concentration of the organic layer was followed by purification by silica gel column chromatography using EtOAc–*n*-hexane, 10%, as an eluent. Yield 850 mg (85%), colorless oil. $[\alpha]_D^{25}$ +79.8 (*c* 0.1,

$CHCl_3$). IR spectrum ($CHCl_3$), ν, cm^{-1}: 1750, 1690, 1644. ^1H NMR spectrum, δ, ppm (*J*, Hz): 0.66 (3H, d, *J* = 8.1, CH_3); 0.76 (3H, d, *J* = 8.1, CH_3); 2.62–2.66 (1H, m, C<u>H</u>$(CH_3)_2$); 3.76 (3H, s, OCH_3); 4.19–4.21 (1H, m, CH); 6.85 (1H, s, CH=); 7.29–7.45 (5H, m, H Ar); 7.52–7.54 (1H, m, H Ar); 7.64–7.66 (1H, m, H Ar); 7.68–7.79 (1H, m, H Ar); 7.81–7.88 (1H, m, H Ar). Found, *m*/*z*: 358.1423 $[M]^+$. $C_{21}H_{21}NNaO_3$. Calculated, *m*/*z*: 358.1414.

Methyl (2*S*)-2-(1-benzyl-3-oxo-1,3-dihydro-2*H*-isoindol-2-yl)-3-methylbutanoate (4). Pd/C (0.1 g, 5 mol %) was added to a solution of methyl (2*S*)-2-[(1*Z*)-1-benzylidene-3-oxo-1,3-dihydro-2*H*-isoindol-2-yl]-3-methylbutanoate (**3**) (1 g, 0.0029 mol) in EtOH (10 ml) under Ar atmosphere, and H_2 gas pressure was applied using H_2 balloon at 25°C. After 1 h, the reaction mixture was filtered and concentrated. Yield 1.1 g (~100%), gummy solid. $[\alpha]_D^{25}$ +12.2 (*c* 0.76, $CHCl_3$). IR spectrum ($CHCl_3$), ν, cm^{-1}: 1760, 1700, 1690, 1650. ^1H NMR spectrum, δ, ppm (*J*, Hz): 0.92 (3H, d, *J* = 8.1, CH_3); 1.02 (3H, d, *J* = 8.1, CH_3); 1.12 (3H, d, *J* = 8.2, CH_3); 1.18 (3H, d, *J* = 8.2, CH_3); 2.53–2.58 (1H, m, $PhCH_2$); 2.61–2.65 (1H, m, $PhCH_2$); 2.71–2.82 (2H, m, 2C<u>H</u>$(CH_3)_2$); 3.61 (1H, dd, *J* = 16.3, *J* = 4.2, $PhCH_2$); 3.75 (3H, s, OCH_3); 3.81 (3H, s, OCH_3); 3.86 (1H, dd, *J* = 7.8, *J* = 2.1, $PhCH_2$); 4.50 (1H, d, *J* = 9.8, *i*-PrCH); 4.61 (1H, d, *J* = 12.0, *i*-PrCH); 4.78–4.83 (2H, m, CHN); 6.49 (2H, d, *J* = 8.0, H Ar); 6.53 (2H, d, *J* = 7.8, H Ar); 7.03–7.09 (2H, m, H Ar); 7.16 (6H, m, H Ar); 7.26–7.31 (2H, m, H Ar); 7.40–7.46 (2H, m, H Ar); 7.78 (2H, m, H Ar). ^{13}C NMR spectrum, δ, ppm: 19.2; 19.7; 20.6 (2C); 28.1; 29.9; 39.1; 39.8; 52.2 (2C); 60.7; 62.0; 62.8; 123.3 (2C); 124.0; 127.1; 127.2; 128.2; 128.3; 128.7 (2C); 129.7; 131.1; 131.2 (2C); 136.6; 137.0; 145.3; 145.4; 168.7; 169.2; 171.0; 171.6. Found, *m*/*z*: 360.1563 $[M]^+$. $C_{21}H_{23}NNaO_3$. Calculated, *m*/*z*: 360.1570.

Methyl (2*S*)-2-[(1*S*)-1-benzyl-3-oxo-1,3-dihydro-2*H*-isoindol-2-yl]-3-methylbutanoate ((*S*,*S*)-4). Crude product was crystallized from *n*-heptane. Yield 350 mg (30%), white crystalls. $[\alpha]_D^{25}$ +20.8 (*c* 0.5, $CHCl_3$). IR spectrum ($CHCl_3$), ν, cm^{-1}: 1740, 1680. ^1H NMR spectrum, δ, ppm (*J*, Hz): 1.02 (3H, d, *J* = 8.1, CH_3); 1.12 (3H, d, *J* = 8.1, CH_3); 2.56–2.62 (1H, m, $PhCH_2$); 2.63–2.65 (1H, m, C<u>H</u>$(CH_3)_2$); 3.81 (3H, s, OCH_3); 3.86–3.90 (1H, m, $PhCH_2$); 4.52 (1H, d, *J* = 9.8, *i*-PrCH); 4.81–4.85 (1H, m, CHN); 6.49 (1H, d, *J* = 8.0, H Ar); 7.03–7.13 (2H, m, H Ar); 7.26–7.31 (5H, m, H Ar); 7.84–7.86 (1H, m, H Ar). ^{13}C NMR spectrum, δ, ppm: 19.2; 20.2; 29.9; 39.8; 52.2; 62.0; 62.8; 123.3; 123.9; 127.1; 128.2; 128.7; 129.7; 131.1; 131.2; 137.0; 145.3; 168.7; 171.0. Found, *m*/*z*: 360.1575 $[M]^+$. $C_{21}H_{23}NNaO_3$. Calculated, *m*/*z*: 360.1570.

Methyl (2*S*)-2-[(1*R*)-1-benzyl-3-oxo-1,3-dihydro-2*H*-isoindol-2-yl]-3-methylbutanoate ((*R*,*S*)-4). Filtrate after atmospheric concentration and recrystallization from *n*-heptane gave compound *(R*,*S*)-**4**. Yield 300 mg (14%), white solid. $[\alpha]_D^{25}$ +6.1 (*c* 0.8, $CHCl_3$). IR spectrum ($CHCl_3$), ν, cm^{-1}: 1725, 1690. ^1H NMR spectrum, δ, ppm (*J*, Hz): 0.92 (3H, d, *J* = 8.1, CH_3); 1.18 (3H, d, *J* = 8.1, CH_3); 2.53–2.60 (1H, m, $PhCH_2$); 2.76–2.80 (1H, m, C<u>H</u>$(CH_3)_2$); 3.61 (1H, dd, *J* = 16.3, *J* = 4.2, $PhCH_2$); 3.75 (3H, s, OCH_3); 4.62 (1H, d, *J* = 12.0, *i*-PrCH); 4.78–4.85 (1H, m, CHN); 6.53 (1H, d, *J* = 8.4, H Ar); 7.16 (1H, d, *J* = 8.4, H Ar); 7.28–7.67 (6H, m, H Ar); 7.76–7.78 (1H, m, H Ar). ^{13}C NMR spectrum, δ, ppm: 19.7; 20.6; 28.7; 39.0; 52.2; 60.6 (2C); 123.3; 124.0; 127.1; 128.3; 128.7; 129.7; 131.1; 131.2; 136.6; 145.4; 169.2; 171.6. Found, *m*/*z*: 360.1585 $[M]^+$. $C_{21}H_{23}NNaO_3$. Calculated, *m*/*z*: 360.1570.

X-ray structural analysis of compound (*S*,*S*)-4. A suitable single crystal was selected using the polarizing microscope and mounted on the Bruker D8 Venture diffractometer system equipped with micro focus Cu source, Photon 100 CMOS detector. Crystal was kept at 298(2) K during the data collection with 0.5 mm scan width and distance 40 mm from crystal to detector. The structure was solved using the Olex2, using Intrinsic Phasing and refined with the XL refinement package using least-squares minimization.[37] The complete crystallographic data for compound (*S*,*S*)-**4** were deposited at the Cambridge Crystallographic Data Center (deposit CCDC 1981423).

Supplementary information file containing ^1H, ^{13}C NMR, and X-ray diffraction data for the selected compounds is available at the journal website at http://link.springer.com/journal/10593.

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