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Enantioselective synthesis of the spirotryprostatin A scaffold

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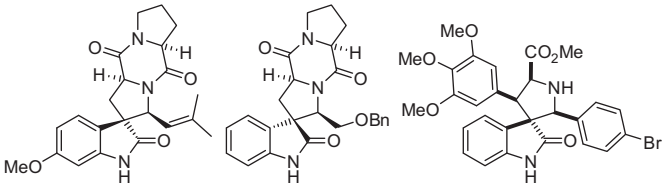
ABSTRACT

The pentacyclic spirotryprostatin scaffold embodies an oxindole with an all-carbon quaternary stereocenter. The scaffold can efficiently be accessed in a one-pot reaction sequence consisting of a highly enantioselective 1,3-dipolar cycloaddition, N-acylation of the resulting stereochemically complex 3,3′-pyrrolidinyl-spirooxindole core with Fmoc-proline and spontaneous ring closure upon N-deprotection.

1. Introduction

Natural products (NPs) are a rich source of evolutionary validated scaffold structures endowed with biological activity. Compound collections inspired by natural products often serve as valuable starting points for medicinal chemistry and chemical biology research.[1] Based on this rationale, we introduced biology-oriented synthesis (BIOS) for the design and synthesis of natural product-based compound libraries with focused structural diversity.[2] Given the structural complexity and richness in stereogenic centres of natural products and compound collections inspired by them, the development of efficient asymmetric methods for their synthesis is in high demand.

The 3,3′-pyrrolidinyl-spirooxindole motif is an important heterocyclic scaffold that forms the core of numerous alkaloids including spirotryprostatin A–E, which display a broad range of biological activities.[3,4] Studies on the synthesis of spirotryprostatin A (**1**) resulted in the discovery of analogue **2**, which shows higher activity than the natural product itself (Fig. 1).[5] In the development of a natural product-inspired compound collection with spirooxindole scaffold, we recently discovered 3,3′-pyrrolidinyl-spirooxindole **3** that arrests mitosis, causes chromosome congression defects and inhibits tubulin re-growth in cells.[6]



spirotryprostatin A (**1**) **2** **3**

Fig. 1. Structures of 3,3′-pyrrolidinyl-spirooxindoles. Bn=benzyl.

The key structural feature of spirotryprostatins is a pentacycle with an all-carbon quaternary spirostereocenter embedded in the oxindole core. The need to construct this centre stereospecifically makes the synthesis of these molecules a challenging task and subject to significant interest.[7,8] Recently developed asymmetric approaches include oxidative rearrangement of chiral tetrahydro-β-carbolins,[5,9] an iminium ion intramolecular cyclization,[10] [3+2][11] and [5+2][12] cycloadditions, intramolecular Heck reactions,[13] a nitroolefination strategy,[14] magnesium iodide catalyzed ring-expansion[15] and a Pd-catalyzed prenylation.[16] In all cases diastereomers were formed. Given the lack of knowledge on the mechanism of action of spirotryprostatins in biological systems, the design and development of methodology allowing for the synthesis of a focused compound collection for subsequent chemical biology research is in high demand.

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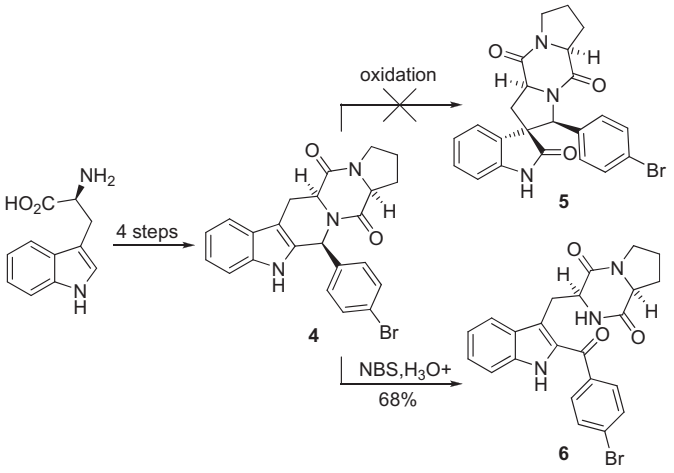
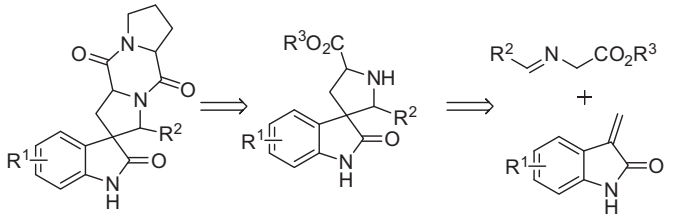
2. Results and discussion

Our initial studies were focused on a linear approach based on the oxidative rearrangement of tetrahydro-β-carbolines.[5,9] Tetrahydro-β-carboline **4** was obtained from L-tryptophan in four steps using a diastereoselective Pictet–Spengler cyclization as key step (Scheme 1). Attempts to rearrange **4** to the spirotryprostatin analogue **5** using various oxidative conditions were not successful and selective formation of the acylindole derivative **6** was observed.



Scheme 1. Oxidation of tetrahydro-β-carboline **4**.

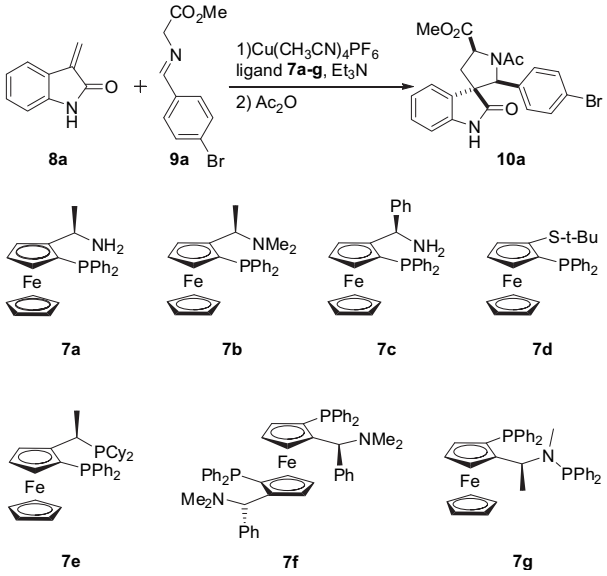
Given this failure we developed a new approach for the preparation of a collection of compounds with the 3,3′-pyrrolidinyl-spirooxindole scaffold embodied in the spirotryprostatins (Scheme 2). Here we report the first example of a catalytic enantioselective cycloaddition of azomethine ylides[17,18] to α,α-disubstituted alkenes giving access to the 3,3′-pyrrolidinyl-spirooxindole core with an all-carbon quaternary spirostereocenter and two tertiary centres in a one-pot transformation from readily accessible starting materials. Spiropyrrolidines with an additional stereocenter (see e.g., **3**) have been synthesized by dipolar cycloadditions employing arylidene- or alkylidene indolinones as dipolarophiles.[6] However, due to their pronounced reactivity α,α-disubstituted alkenes[19] have not been used successfully in this enantioselective catalytic [3+2] cycloaddition, and the spirotryprostatin core has not been accessible with this methodology so far.



Scheme 2. Retrosynthesis of spirotryprostatin A analogues.

The synthesis of 3,3′-pyrrolidinyl-spirooxindoles commenced with the cycloaddition of *N*-(4-bromobenzylidene)glycine methyl ester **9a** with 3-methyleneoxindole **8a** using ferrocene-based ligands 7**a**–**g** and $Cu(CH_3CN)_4PF_6$ (Table 1). The reaction proceeded smoothly at ambient temperature in the presence of 5 mol % of the Cu(I)/ligand complex. The nitrogen of the pyrrolidine was selectively protected prior to workup to prevent isomerisation of the 3,3′-pyrrolidinyl-spirooxindoles due to retro-Mannich/Mannich[20] equilibration. Initial screening of various ligands revealed that the best results were obtained for the formation of **10a** with regard to

Table 1
Evaluation of different reaction conditions for the 1,3-dipolar cycloaddition



Entry[a]	Ligand	Solvent	Time (h)	Yield[b] (%)	dr[c]	ee[d] (%)
1	**7a**	DCM	1.5	60	1/20	88
2	**7b**	DCM	1	51	1/6	56[e]
3	**7c**	DCM	1	72	1/20	65
4	**7d**	DCM	1	56	1/15	91[e]
5	**7e**	DCM	1	63	1/20	62[e]
6	**7f**	DCM	1	63	1/5	69
7	**7g**	DCM	2	78	1/20	45[e]
8	**7d**	THF	3	33	1/10	95[e]
9	**7d**	Toluene	12	Traces	n.d.	n.d.
10	**7d**	Et_2O	12	Traces	n.d.	n.d.
11[f]	**7d**	DCM	1	53	1/15	90[e]
12[g]	**7d**	DCM	0.8	52	1/15	94[e]
13[h]	**7d**	DCM	3	45	1/12	71[e]
14[i]	**7d**	DCM	4	51	1/18	95[e]
15[j]	**7d**	DCM	2	56	1/18	95[e]

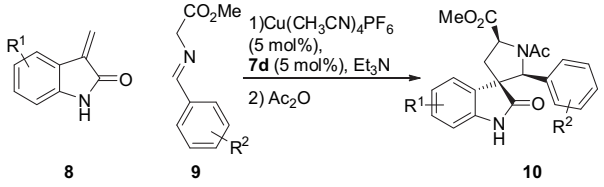
n.d.=not determined.
[a] Reaction conditions: iminoester **9a** (1.0 equiv) was reacted with 3-methyleneoxindole **8a** (1.5 equiv), $Cu(CH_3CN)_4PF_6$ (5 mol %), ligand **7a**–**g** (5 mol %) in dichloromethane (0.1 M) at ambient temperature for the given time. Then acetic anhydride (1.05 equiv) was added.
[b] Isolated yields of the major diastereomer after column chromatography.
[c] Determined by ^1H NMR analysis.
[d] Determined by HPLC analysis.
[e] Opposite enantiomer.
[f] 10 mol % of ligand **7d** was used.
[g] 10 mol % of $Cu(CH_3CN)_4PF_6$ and 10 mol % of ligand **7d** were used.
[h] 3 mol % of $Cu(CH_3CN)_4PF_6$ and 3 mol % of ligand **7d** were used.
[i] Performed at 0 °C.
[j] Performed for 30 min at 0 °C and then the reaction mixture was allowed to warm to ambient temperature.

enantiomeric excess, diastereoselectivity and yield when the *S*,*P*-ferrocenyl ligand **7d** was used in dichloromethane (Table 1, entry 4).

To further optimize the reaction conditions, we varied the solvent, concentration of the reactants, reaction temperature, ligand/catalyst ratio and catalyst loading. We found that cycloaddition in tetrahydrofuran leads to the product with comparable enantioselectivity but lower yields. Similar trends were observed at lower reaction temperature and higher ligand/catalyst loading (Table 1, entries 11 and 14). Nonpolar solvents such as toluene led to the formation of only trace amounts of product most likely due to low solubility of the 3-methyleneoxindole. The reduction of ligand/catalyst loading to 3 mol % (Table 1, entry 13) compromised chemical yield and enantioselectivity. Best results were obtained when the reaction was started at 0 °C for 30 min and continued at ambient temperature until the iminoester **9a** was consumed (Table 1, entry 15).[21]

With the optimized reaction conditions in hand, we investigated the substrate scope of the 1,3-dipolar cycloaddition with regard to the substitution on the azomethine ylides and 3-methyleneoxindoles (Table 2). A variety of mono- and polysubstituted benzylidene glycine derivatives bearing electron-withdrawing and electron-donating substituents reacted with excellent

Table 2
Scope of the catalytic enantioselective cycloaddition of azomethine ylides to 3-methyleneoxindoles



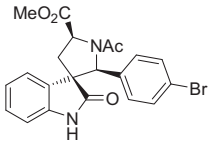
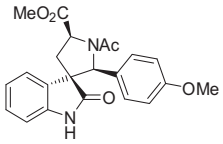
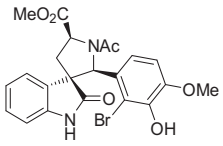
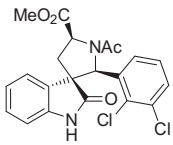
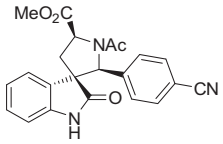
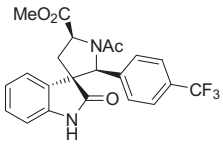
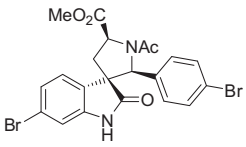
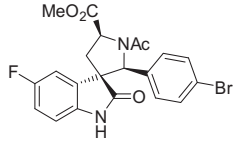
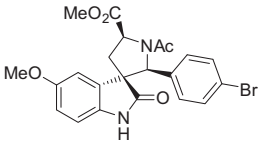
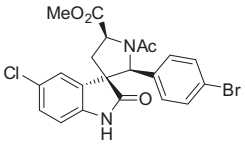
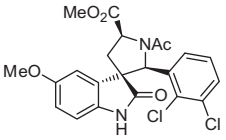
Entry		Product	Yield[a] (%)	dr[b]	ee[c] (%)
1	**10a**		56	1/18	95
2	**10b**		53	1/20	84
3	**10c**		41	1/2	93
4	**10d**		40	1/2	87
5	**10e**		41	1/2	92
6	**10f**		69	1/20	92
7	**10g**		51	1/20	96
8	**10h**		60	1/20	95

Table 2 (*continued*)

Entry		Product	Yield[a] (%)	dr[b]	ee[c] (%)
9	**10i**		55	1/20	97
10	**10j**		40	1/20	93
11	**10k**		45	1/2	96

[a] Isolated yields of the single diastereomer after column chromatography.
[b] Determined by ^{1}H NMR analysis.
[c] Determined by HPLC analysis.

enantioselectivity. Except for *ortho*-substituted azomethine ylides the diastereoselectivity was high. The products were isolated as single diastereomers in high yields after two steps. Excellent results independent of the electronic nature of the substituent were obtained for the different 3-methyleneoxindoles. Interestingly, the reaction worked well in the presence of acidic groups such as phenol (Table 2, entry 3) and did not require protection of the nitrogen of the 3-methyleneoxindoles. The absolute configuration of the major stereoisomer was unambiguously determined by crystal structure analysis (Fig. 2).

Following the one-pot procedure developed for azomethine ylides and 3-methyleneoxindoles **8**, we next applied this methodology to the enantioselective construction of the biologically relevant but stereochemically complex spirotryprostatin A analogues **11**. The one-pot synthesis included an enantioselective 1,3-dipolar cycloaddition, acylation of the hindered amine with (*L*)-FmocProCl and deprotection of the Fmoc-group, which resulted immediately

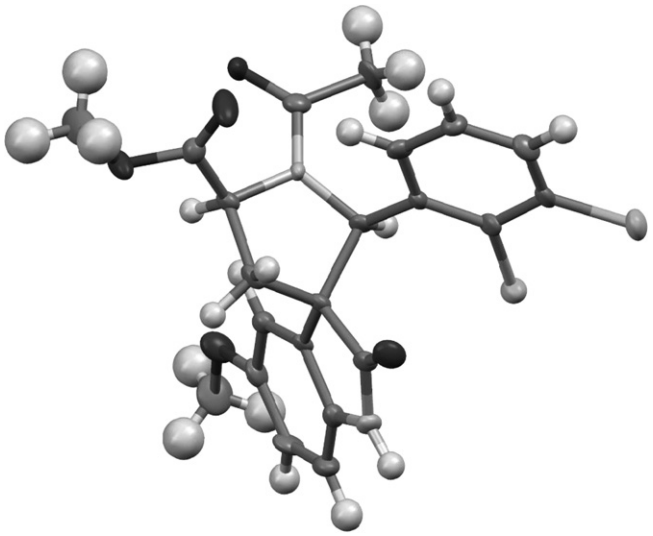
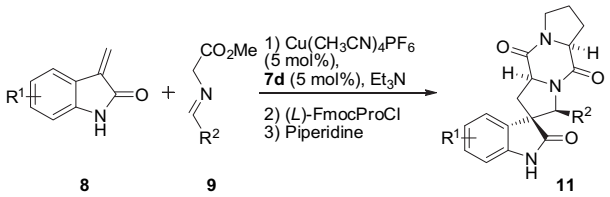
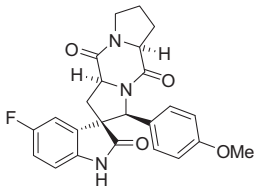
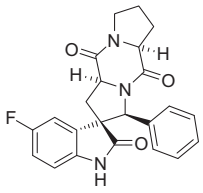
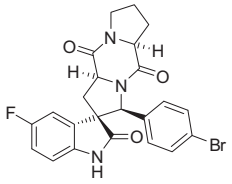
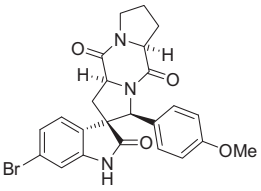
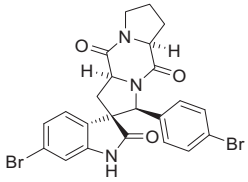
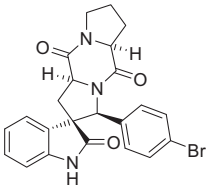


Fig. 2. ORTEP plot of **10k** at 50% probability level.

Table 3
Spirotryprostatin A analogues obtained by the one-pot procedure



8 **9** **11**

Product, yield (%)[a]	Product, yield (%)[a]
 **11a**, 60%	 **11b**, 63%
 **11c**, 18%	 **11d**, 55%
 **11e**, 21%	 **11f**, 45%

[a] Isolated yields after column chromatography.

in triggering of a diketopiperazine cyclization to form the pentacyclic scaffold (Table 3). The desired products **11** were obtained in a one-pot procedure from readily accessible compounds. Notably, the approach developed here gives access to spirotryprostatin analogues that could not be obtained by application of known methods (see above).

3. Conclusion

In conclusion, we have developed a highly enantioselective and high yielding synthesis of the polycyclic spirotryprostatin scaffold embodying the 3,3′-pyrrolidinyl-spirooxindole core by means of a catalytic [3+2] cycloaddition of azomethine ylides. The synthesis is efficient and highly practical and should give ready access to a natural product-inspired compound collection based on the spirotryprostatin structure.

4. Experimental section

4.1. General

Unless otherwise noted, all commercially available compounds were used as provided without further purification. Solvents for chromatography were technical grade and distilled prior to use. Dry solvents (CH_2Cl_2, toluene and THF) were purified by the Solvent Purification System M-BRAUN Glovebox Technology SPS-800. Analytical thin-layer chromatography (TLC) was performed on Merck silica gel aluminium plates with F-254 indicator, visualised by irradiation with UV light. Column chromatography was performed using silica gel Merck 60 (particle size 0.040–0.063 mm). Solvent mixtures are understood as volume/volume.

^{1}H NMR and ^{13}C NMR were recorded on a Bruker DRX400 (400 MHz) or DRX500 (500 MHz) spectrometer in $CDCl_3$, $(CD_3)_2SO$ or CD_3OD. Data are reported in the following order: chemical shift (δ) in parts per million; multiplicities are indicated br s (broadened singlet), s (singlet), d (doublet), t (triplet), m (multiplet); coupling constants (J) are given in Hertz (Hz). High resolution mass spectra were recorded on an LTQ Orbitrap mass spectrometer coupled to an Accela HPLC-System (HPLC column: Hypersyl GOLD, 50 mm×1 mm, 1.9 μm). Fourier transform infrared spectroscopy (FTIR) spectra were obtained with a Bruker Tensor 27 spectrometer (ATR, neat) and are reported in terms of frequency of absorption (cm^{-1}). Optical rotations were measured in a Schmidt+Haensch Polartronic HH8 polarimeter.

The enantiomeric excesses were determined by HPLC analysis using a chiral stationary phase column (column: CHIRALCEL IA, eluent: isohexane/(ethanol/DCM=1/100)). The chiral HPLC methods were calibrated with the corresponding racemic mixtures. Chemical yields refer to pure isolated substances. The yields and enantiomeric excesses are given in Table 2.

4.2. Synthetic protocols

4.2.1. General procedure for the enantioselectively catalyzed 1,3-dipolar cycloaddition. To a solution of iminoester (0.10 mmol), (*Rp*)-2-(*tert*-butylthio)-1-(diphenylphosphino)ferrocene (5 mol %, 5 μmol) and tetrakis(acetonitrile)copper(I) hexafluorophosphate (5 mol %, 5 μmol) in dichloromethane (1 mL) at 0 °C under argon were added triethylamine (1.1 equiv, 0.11 mmol) and 3-methyleneoxindole (1.5 equiv, 0.15 mmol). The reaction mixture was allowed to stir for 30 min at 0 °C and then at ambient temperature. Acetic anhydride (1.05 equiv, 0.105 mmol) was added to the reaction mixture when the iminoester was consumed. The reaction was stirred additionally at ambient temperature for 2 h. The solvent was removed in vacuo and purification of the crude product by column chromatography on silica gel (ethyl acetate/pentane) afforded the pure product.

*4.2.2. Methyl (2′S,3R,5′S)-1′-acetyl-2′-(4-bromophenyl)-2-oxo-1,2-dihydrospiro[indole-3,3′-pyrrolidine]-5′-carboxylate (**10a**).* ^{1}H NMR (400 MHz, $CDCl_3$, # denotes major-, * minor rotamer signals) δ=9.08$^{\#}$ (s, 1H), 8.52* (s, 1H), 7.40–7.05 (m, 7H), 6.85$^{\#}$ (d, J=7.7, 1H), 6.69* (d, J=7.7, 2H), 5.29* (s, 1H), 5.07$^{\#}$ (dd, J=8.1, 7.9, 1H), 5.00$^{\#}$ (s, 1H), 4.86* (m, 1H), 3.92* (s, 3H), 3.86$^{\#}$ (s, 3H), 2.93* (d, J=13.4, 1H), 2.79* (dd, J=13.4, 9.4, 1H), 2.71$^{\#}$ (dd, J=13.0, 7.7, 1H), 2.45$^{\#}$ (dd, J=13.0, 8.1, 1H), 2.24* (s, 3H), 1.83$^{\#}$ ppm (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$, major rotamer) δ=176.88, 171.75, 171.37, 140.55, 136.81, 132.08, 131.93, 131.26, 129.82, 129.22, 127.93, 123.79, 122.81, 122.61, 110.99, 71.72, 59.83, 59.04, 52.99, 36.52, 22.92 ppm; FTIR: $\tilde{\nu}$=2951, 1718, 1651, 1615, 1489, 1472, 1434, 1399, 1375, 1337, 1297, 1240, 1204, 1181, 1130, 1102, 1071, 1043, 1010 cm^{-1}; HRMS: calcd for $[M+H]^+$ $C_{21}H_{20}{}^{79}BrN_2O_4$: 443.06010, found: 443.05997; HRMS: calcd for $[M+H]^+$ $C_{21}H_{20}{}^{81}BrN_2O_4$: 445.05805, found: 445.05768; $[\alpha]_D^{RT}$ −81.8 ($CHCl_3$, *c* 1.0); HPLC conditions: CHIRALCEL IA column, isohexane/(ethanol/DCM=1/100)=2/3, flow rate=0.5 mL min^{-1}, major enantiomer: t_R=24.5 min; minor enantiomer: t_R=31.0 min.

*4.2.3. Methyl (2′S,3R,5′S)-1′-acetyl-2′-(4-methoxyphenyl)-2-oxo-1,2-dihydrospiro[indole-3,3′-pyrrolidine]-5′-carboxylate (**10b**).* ^{1}H NMR (500 MHz, $CDCl_3$) δ=8.67 (s, 1H), 7.38–7.21 (m, 4H), 7.13 (t, J=7.5,

1H), 6.84 (d, J=7.7, 1H), 6.76 (d, J=8.4, 2H), 5.08 (dd, J=8.2, 7.4, 1H), 4.98 (s, 1H), 3.87 (s, 3H), 3.71 (s, 3H), 2.76 (dd, J=13.0, 7.4, 1H), 2.45 (dd, J=13.0, 8.2, 1H), 1.83 ppm (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ=176.93, 171.78, 171.51, 159.70, 140.75, 132.47, 129.54, 129.49, 128.61, 123.51, 122.81, 114.12, 110.74, 72.20, 59.85, 59.14, 55.42, 52.84, 36.44, 22.85 ppm; FTIR: $\tilde{\nu}$=3215, 2955, 1720, 1617, 1513, 1472, 1437, 1400, 1339, 1289, 1246, 1205, 1177, 1108, 1032 cm^{-1}; HRMS: calcd for $[M+H]^+$ $C_{22}H_{22}N_2O_5$: 395.16015, found: 395.15964; $[\alpha]_D^{RT}$ −49.8 ($CHCl_3$, *c* 1.0); HPLC conditions: CHIRALCEL IA column, isohexane/(ethanol/DCM=1/100)=2/3, flow rate=0.5 mL min^{-1}, major enantiomer: t_R=27.5 min; minor enantiomer: t_R=31.4 min.

*4.2.4. Methyl (2′R,3R,5′S)-1′-acetyl-2′-(2-bromo-3-hydroxy-4-methoxyphenyl)-2-oxo-1,2-dihydrospiro[indole-3,3′-pyrrolidine]-5′-carboxylate (**10c**).* ^{1}H NMR (400 MHz, CD_3OD) δ=7.87 (d, J=8.6, 1H), 7.36–7.29 (m, 1H), 7.21 (d, J=7.2, 1H), 7.17–7.09 (m, 1H), 7.03 (d, J=8.6, 1H), 6.97 (d, J=7.7, 1H), 5.49 (s, 1H), 4.92–4.85 (m, 1H), 3.93 (s, 3H), 3.85 (s, 3H), 2.64–2.55 (m, 1H), 2.36–2.30 (m, 1H), 1.82 ppm (s, 3H); ^{13}C NMR (101 MHz, CD_3OD) δ=175.75, 172.18, 172.08, 148.31, 144.03, 141.05, 133.46, 129.09, 129.03, 123.02, 122.35, 120.07, 110.71, 110.20, 110.03, 70.36, 59.35, 57.55, 55.67, 51.99, 37.36, 21.00 ppm; FTIR: $\tilde{\nu}$=2953, 1719, 1642, 1619, 1490, 1471, 1439, 1401, 1369, 1333, 1276, 1203, 1151, 1106, 1079, 1031 cm^{-1}; HRMS: calcd for $[M+H]^+$ $C_{22}H_{21}{}^{79}BrN_2O_6$: 489.06558, found: 489.06517; HRMS: calcd for $[M+H]^+$ $C_{22}H_{21}{}^{81}BrN_2O_6$: 491.06353, found: 491.06298; $[\alpha]_D^{RT}$ −26.7 ($CHCl_3$, *c* 1.0); HPLC conditions: CHIRALCEL IA column, isohexane/(ethanol/DCM=1/100)=1/3, flow rate=0.5 mL min^{-1}, major enantiomer: t_R=18.3 min; minor enantiomer: t_R=35.5 min.

*4.2.5. Methyl (2′R,3R,5′S)-1′-acetyl-2′-(2,3-dichlorophenyl)-2-oxo-1,2-dihydrospiro[indole-3,3′-pyrrolidine]-5′-carboxylate (**10d**).* ^{1}H NMR (500 MHz, $CDCl_3$) δ=8.45 (dd, J=7.8, 1.2, 1H), 8.32 (s, 1H), 7.49 (dd, J=7.9, 1.4, 1H), 7.42 (t, J=7.9, 1H), 7.35 (td, J=7.6, 1.2, 1H), 7.20–7.11 (m, 2H), 6.92 (d, J=7.8, 1H), 5.46 (s, 1H), 4.94 (dd, J=11.5, 7.0, 1H), 3.88 (s, 3H), 2.67–2.58 (m, 1H), 2.32 (dd, J=12.7, 7.0, 1H), 1.88 ppm (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ=174.91, 172.06, 171.05, 139.89, 137.55, 133.10, 133.00, 131.60, 130.54, 129.64, 128.46, 128.33, 123.78, 122.65, 110.69, 68.63, 59.26, 57.34, 53.05, 37.69, 22.48 ppm; FTIR: $\tilde{\nu}$=3235, 2925, 2853, 1745, 1721, 1639, 1619, 1471, 1444, 1424, 1367, 1330, 1293, 1241, 1204, 1186, 1159, 1107, 1080, 1043, 1009 cm^{-1}; HRMS: calcd for $[M+H]^+$ $C_{21}H_{18}{}^{35}Cl_2N_2O_4$: 433.07164, found: 433.07153; HRMS: calcd for $[M+H]^+$ $C_{21}H_{18}{}^{35}Cl{}^{37}ClN_2O_4$: 435.06869, found: 435.06849; $[\alpha]_D^{RT}$ +7.1 ($CHCl_3$, *c* 1.0); HPLC conditions: CHIRALCEL IA column, isohexane/(ethanol/DCM=1/100)=1/1, flow rate=0.5 mL min^{-1}, major enantiomer: t_R=21.7 min; minor enantiomer: t_R=25.8 min.

*4.2.6. Methyl (2′S,3R,5′S)-1′-acetyl-2′-(4-cyanophenyl)-2-oxo-1,2-dihydrospiro[indole-3,3′-pyrrolidine]-5′-carboxylate (**10e**).* ^{1}H NMR (500 MHz, $CDCl_3$, # denotes major-, * minor rotamer signals) δ=8.41$^{\#}$ (s, 1H), 7.87* (s, 1H), 7.66–7.51$^{\#*}$ (m, 2H), 7.43–7.09$^{\#*}$ (m, 5H), 6.86$^{\#}$ (d, J=7.7, 1H), 6.73* (d, J=7.7, 1H), 5.35$^{\#}$ (s, 1H), 5.15–5.02$^{\#*}$ (m, 2H), 4.88* (d, J=8.9, 1H), 3.92* (s, 3H), 3.88$^{\#}$ (s, 3H), 2.94* (d, J=13.4, 1H), 2.82* (dd, J=13.4, 9.4, 1H), 2.72$^{\#}$ (dd, J=13.0, 8.0, 1H), 2.47$^{\#}$ (dd, J=13.0, 8.1, 1H), 2.26* (s, 3H), 1.83$^{\#}$ ppm (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$, mixture of the rotamers) δ=178.09, 175.84, 171.73, 171.38, 171.05, 171.00, 143.20, 142.56, 141.34, 140.27, 132.67, 132.07, 131.98, 130.08, 129.99, 129.21, 128.33, 126.99, 124.01, 123.82, 123.36, 122.89, 119.24, 118.86, 112.59, 111.37, 110.80, 110.52, 71.64, 71.18, 61.55, 59.82, 59.07, 57.86, 53.19, 53.03, 38.61, 36.91, 23.11, 22.84 ppm; FTIR: $\tilde{\nu}$=2955, 1721, 1646, 1619, 1504, 1472, 1436, 1402, 1339, 1273, 1205, 1177, 1107, 1067, 1040, 1019 cm^{-1}; HRMS: calcd for $[M+H]^+$ $C_{22}H_{19}N_3O_4$: 390.14483, found: 390.14501; $[\alpha]_D^{RT}$ −40.4 ($CHCl_3$, *c* 1.0); HPLC conditions: CHIRALCEL IA column, isohexane/(ethanol/DCM=1/100)=2/3, flow rate=0.5 mL min^{-1}, major enantiomer: t_R=28.3 min; minor enantiomer: t_R=31.1 min.

*4.2.7. Methyl (2′S,3R,5′S)-1′-acetyl-2-oxo-2′-[4-(trifluoromethyl)phenyl]-1,2-dihydrospiro[indole-3,3′-pyrrolidine]-5′-carboxylate (**10f**).* ^{1}H NMR (400 MHz, $CDCl_3$, # denotes major-, * minor rotamer signals) δ=8.77$^{\#}$ (s, 1H), 8.18* (s, 1H), 7.64–7.07$^{\#*}$ (m, 7H), 6.83$^{\#}$ (d, J=7.7, 1H), 6.68* (d, J=7.7, 1H), 5.38* (s, 1H), 5.09$^{\#}$ (dd, J=8.1, 7.8, 1H), 5.06$^{\#}$ (s, 1H), 4.88* (m, 1H), 3.92* (s, 3H), 3.87$^{\#}$ (s, 3H), 2.94* (d, J=13.3, 1H), 2.86–2.77* (m, 1H), 2.73$^{\#}$ (dd, J=13.0, 7.8, 1H), 2.46$^{\#}$ (dd, J=13.0, 8.1, 1H), 2.26* (s, 3H), 1.81$^{\#}$ ppm (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$, mixture of the rotamers) δ=178.60, 176.41, 171.71, 171.46, 171.25, 171.15, 141.75, 141.46, 141.05, 140.41, 131.97, 129.92, 129.86, 129.32, 127.87, 126.46, 125.77, 125.19, 125.16, 123.88, 123.70, 123.32, 122.82, 110.83, 110.61, 71.61, 71.15, 61.62, 59.82, 59.03, 57.90, 53.18, 53.02, 38.50, 36.75, 23.26, 22.87 ppm; FTIR: $\tilde{\nu}$=2953, 1721, 1654, 1619, 1473, 1399, 1323, 1272, 1205, 1163, 1112, 1066, 1018 cm^{-1}; HRMS: calcd for $[M+H]^+$ $C_{22}H_{19}F_3N_2O_4$: 433.13697, found: 433.13667; $[\alpha]_D^{RT}$ −39.1 ($CHCl_3$, *c* 1.0); HPLC conditions: CHIRALCEL IA column, isohexane/(ethanol/DCM=1/100)=2/3, flow rate=0.5 mL min^{-1}, major enantiomer: t_R=19.5 min; minor enantiomer: t_R=21.9 min.

*4.2.8. Methyl (2′S,3R,5′S)-1′-acetyl-6-bromo-2′-(4-bromophenyl)-2-oxo-1,2-dihydrospiro[indole-3,3′-pyrrolidine]-5′-carboxylate (**10g**).* ^{1}H NMR (500 MHz, $CDCl_3$, # denotes major-, * minor rotamer signals) δ=8.44$^{\#}$ (s, 1H), 7.95* (s, 1H), 7.48–6.83$^{\#*}$ (m, 7H), 5.27* (s, 1H), 5.06$^{\#}$ (dd, J=8.4, 7.0 1H), 4.97$^{\#}$ (s, 1H), 4.85* (m, 1H), 3.92* (s, 3H), 3.88$^{\#}$ (s, 3H), 2.93* (d, J=13.0, 1H), 2.80–2.74* (m, 1H), 2.74$^{\#}$ (dd, J=13.0, 7.0, 1H), 2.45$^{\#}$ (dd, J=13.0, 8.4, 1H), 2.24* (s, 3H), 1.83$^{\#}$ ppm (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$, major rotamer) δ=176.13, 171.48, 171.26, 141.81, 136.37, 132.09, 131.44, 130.85, 129.11, 127.83, 126.65, 124.21, 123.36, 122.95, 114.15, 71.69, 59.80, 58.84, 53.02, 36.55, 22.88 ppm; FTIR: $\tilde{\nu}$=2951, 1726, 1645, 1610, 1484, 1435, 1403, 1331, 1202, 1180, 1118, 1059, 1041, 1010 cm^{-1}; HRMS: calcd for $[M+H]^+$ $C_{21}H_{18}{}^{79}Br_2N_2O_4$: 520.97061, found: 520.97035; HRMS: calcd for $[M+H]^+$ $C_{21}H_{18}{}^{79}Br{}^{81}BrN_2O_4$: 522.96856, found: 522.96805; HRMS: calcd for $[M+H]^+$ $C_{21}H_{18}{}^{81}Br_2N_2O_4$: 524.96652, found: 524.96593; $[\alpha]_D^{RT}$ −106.8 ($CHCl_3$, *c* 1.0); HPLC conditions: CHIRALCEL IA column, isohexane/(ethanol/DCM=1/100)=2/3, flow rate=0.5 mL min^{-1}, major enantiomer: t_R=28.2 min; minor enantiomer: t_R=40.0 min.

*4.2.9. Methyl (2′S,3R,5′S)-1′-acetyl-2′-(4-bromophenyl)-5-fluoro-2-oxo-1,2-dihydrospiro[indole-3,3′-pyrrolidine]-5′-carboxylate (**10h**).* ^{1}H NMR (500 MHz, $CDCl_3$, # denotes major-, * minor rotamer signals) δ=8.66$^{\#}$ (s, 1H), 8.11* (s, 1H), 7.45–6.88$^{\#*}$ (m, 6H), 6.80$^{\#}$ (dd, J=8.3, 4.0, 1H), 6.66* (m, 1H), 5.26* (s, 1H), 5.06$^{\#}$ (dd, J=8.2, 7.2, 1H), 4.99$^{\#}$ (s, 1H), 4.86* (m, 1H), 3.92* (s, 3H), 3.87$^{\#}$ (s, 3H), 2.95* (d, J=13.8, 1H), 2.80–2.74* (m, 1H), 2.74$^{\#}$ (dd, J=13.1, 7.2, 1H), 2.46$^{\#}$ (dd, J=13.0, 8.2, 1H), 2.24* (s, 3H), 1.84$^{\#}$ ppm (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$, major rotamer) δ=176.56, 171.53, 171.15, 136.57, 136.42, 133.35, 132.02, 131.35, 129.24, 129.19, 127.93, 122.80, 116.37, 116.19, 111.59, 111.53, 111.51, 111.13, 110.93, 71.66, 59.77, 59.57, 52.97, 36.51, 22.88 ppm; FTIR: $\tilde{\nu}$=3206, 2927, 1742, 1722, 1639, 1622, 1484, 1447, 1433, 1402, 1370, 1301, 1280, 1240, 1211, 1175, 1134, 1073, 1031, 1009 cm^{-1}; HRMS: calcd for $[M+H]^+$ $C_{21}H_{18}{}^{79}BrFN_2O_4$: 461.05067, found: 431.05052; HRMS: calcd for $[M+H]^+$ $C_{21}H_{18}{}^{81}BrFN_2O_4$: 463.04863, found: 463.04832; $[\alpha]_D^{RT}$ −73.0 ($CHCl_3$, *c* 1.0); HPLC conditions: CHIRALCEL IA column, isohexane/(ethanol/DCM=1/100)=2/3, flow rate=0.5 mL min^{-1}, major enantiomer: t_R=28.4 min; minor enantiomer: t_R=35.2 min.

*4.2.10. Methyl (2′S,3R,5′S)-1′-acetyl-2′-(4-bromophenyl)-5-methoxy-2-oxo-1,2-dihydrospiro[indole-3,3′-pyrrolidine]-5′-carboxylate (**10i**).* ^{1}H NMR (400 MHz, $CDCl_3$, # denotes major-, * minor rotamer

signals) δ=8.81$^{\#}$ (s, 1H), 8.21* (s, 1H), 7.40–6.80$^{\#*}$ (m, 6H), 6.76$^{\#}$ (d, J=8.4, 1H), 6.62* (d, J=8.5, 1H), 5.27* (s, 1H), 5.07$^{\#}$ (dd, J=8.2, 7.4, 1H), 4.99$^{\#}$ (s, 1H), 4.85* (m, 1H), 3.91* (s, 3H), 3.86$^{\#}$ (s, 3H), 3.85* (s, 3H), 3.84$^{\#}$ (s, 3H), 2.93* (d, J=13.5, 1H), 2.81–2.72* (m, 1H), 2.71$^{\#}$ (dd, J=13.1, 7.4, 1H), 2.45$^{\#}$ (dd, J=13.1, 8.2, 1H), 2.25* (s, 3H), 1.83$^{\#}$ ppm (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$, major rotamer) δ=176.75, 171.72, 171.22, 156.81, 136.84, 133.83, 133.28, 131.91, 131.25, 129.19, 127.94, 122.60, 113.66, 111.31, 110.45, 71.80, 59.84, 59.54, 56.35, 52.97, 36.54, 22.94 ppm; FTIR: $\tilde{\nu}$=2952, 1716, 1650, 1490, 1437, 1400, 1328, 1301, 1273, 1242, 1202, 1179, 1157, 1102, 1071, 1032, 1010 cm^{-1}; HRMS: calcd for $[M+H]^+$ $C_{22}H_{21}{}^{79}BrN_2O_5$: 473.07066, found: 473.07041; HRMS: calcd for $[M+H]^+$ $C_{22}H_{21}{}^{81}BrN_2O_5$: 475.06861, found: 475.06844; $[\alpha]_D^{RT}$ −101.2 ($CHCl_3$, c 1.0); HPLC conditions: CHIRALCEL IA column, isohexane/(ethanol/DCM=1/100)=2/3, flow rate=0.5 mL min^{-1}, major enantiomer: t_R=33.2 min; minor enantiomer: t_R=47.1 min.

*4.2.11. Methyl (2′S,3R,5′S)-1′-acetyl-2′-(4-bromophenyl)-5-chloro-2-oxo-1,2-dihydrospiro[indole-3,3′-pyrrolidine]-5′-carboxylate (**10j**).* ^{1}H NMR (400 MHz, $CDCl_3$, # denotes major-, * minor rotamer signals) δ=8.98$^{\#}$ (s, 1H), 8.43* (s, 1H), 7.44–7.16$^{\#*}$ (m, 6H), 6.77$^{\#}$ (d, J=8.3, 1H), 6.63* (d, J=8.2, 1H), 5.26* (s, 1H), 5.05$^{\#}$ (dd, J=8.2, 7.4, 1H), 4.99$^{\#}$ (s, 1H), 4.85* (m, 1H), 3.90* (s, 3H), 3.86$^{\#}$ (s, 3H), 2.92* (d, J=13.4, 1H), 2.81–2.73* (m, 1H), 2.72$^{\#}$ (dd, J=13.1, 7.4, 1H), 2.45$^{\#}$ (dd, J=13.1, 8.2, 1H), 2.23* (s, 3H), 1.82$^{\#}$ ppm (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$, major rotamer) δ=176.50, 171.59, 171.27, 139.13, 136.55, 133.54, 132.02, 131.35, 129.87, 129.16, 129.07, 127.89, 123.33, 122.79, 111.99, 71.52, 59.82, 59.35, 53.05, 36.50, 22.96 ppm; FTIR: $\tilde{\nu}$=2951, 1723, 1649, 1621, 1480, 1435, 1400, 1327, 1301, 1204, 1180, 1119, 1073, 1034, 1011 cm^{-1}; HRMS: calcd for $[M+H]^+$ $C_{21}H_{18}{}^{79}Br^{35}ClN_2O_4$: 477.02116, found: 477.02076; HRMS: calcd for $[M+H]^+$ $C_{21}H_{18}{}^{79}Br^{37}ClN_2O_4$: 479.01817, found: 479.01823; HRMS: calcd for $[M+H]^+$ $C_{21}H_{18}{}^{81}Br^{37}ClN_2O_4$: 481.01613, found: 481.01543; $[\alpha]_D^{RT}$ −126.3 ($CHCl_3$, c 1.0); HPLC conditions: CHIRALCEL IA column, isohexane/(ethanol/DCM=1/100)=2/3, flow rate=0.5 mL min^{-1}, major enantiomer: t_R=25.9 min; minor enantiomer: t_R=33.9 min.

*4.2.12. Methyl (2′R,3R,5′S)-1′-acetyl-2′-(2,3-dichlorophenyl)-5-methoxy-2-oxo-1,2-dihydrospiro[indole-3,3′-pyrrolidine]-5′-carboxylate (**10k**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ=8.89 (s, 1H), 8.44 (dd, J=7.9, 1.3, 1H), 7.47 (dd, J=7.9, 1.3, 1H), 7.40 (t, J=7.9, 1H), 6.86 (dd, J=8.5, 2.3, 1H), 6.80–6.74 (m, 2H), 5.44 (s, 1H), 4.91 (dd, J=11.4, 7.0, 1H), 3.87 (s, 3H), 3.82 (s, 3H), 2.65–2.54 (m, 1H), 2.31 (dd, J=12.7, 7.0, 1H), 1.87 ppm (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ=175.17, 171.89, 170.77, 156.54, 137.46, 134.00, 133.19, 132.80, 131.41, 130.20, 128.20, 128.09, 113.13, 111.00, 110.10, 68.31, 58.98, 57.69, 56.06, 52.88, 37.35, 22.30 ppm; FTIR: $\tilde{\nu}$=2995, 2947, 2826, 1748, 1718, 1629, 1483, 1454, 1423, 1309, 1199, 1044 cm^{-1}; $[\alpha]_D^{RT}$ +5.1 ($CHCl_3$, c 1.0); HPLC conditions: CHIRALCEL IA column, isohexane/(ethanol/DCM=1/100)=1/1, flow rate=0.5 mL min^{-1}, major enantiomer: t_R=25.6 min; minor enantiomer: t_R=28.0 min.

4.2.13. General procedure for the one-pot synthesis of spirotryprostatin A inspired compounds. To a solution of iminoester **7a** (1 equiv), (*Rp*)-2-(*tert*-butylthio)-1-(diphenylphosphino)ferrocene (5 mol %) and tetrakis (acetonitrile)copper(I) hexafluorophosphate (5 mol %) in dichloromethane (0.1 M) at 0 °C under argon were added triethylamine (1.1 equiv) and 3-methyleneoxindole (1.5 equiv). The reaction mixture was allowed to stir for 30 min at 0 °C and then 2 h at ambient temperature. A solution of (*L*)-FmocProCl in dichloromethane (0.14 M, 1.05 equiv) was added, the reaction mixture was stirred at ambient temperature for 3 h and piperidine (25 equiv) was added. The reaction mixture was stirred at ambient temperature for 5 h and the solvents were removed in vacuo. Purification of the crude product by column chromatography on silica gel (ethyl acetate/pentane=1/3→ethyl acetate) afforded the pure product.

*4.2.14. (2R,3S,5aS,10aS)-5′-Fluoro-3-(4-methoxyphenyl)-5a,6,7,8-tetrahydro-1H,5H-spiro[dipyrrolo[1,2-a:1′,2′-d]pyrazine-2,3′-indole]-2′,5,10(1′H,10aH)-trione (**11a**).* ^{1}H NMR (400 MHz, DMSO) δ=10.35 (s, 1H), 7.48 (dd, J=8.7, 2.5, 1H), 7.08 (td, J=9.6, 2.5, 1H), 6.83 (dd, J=8.5, 4.5, 1H), 6.76 (s, 4H), 5.05 (dd, J=10.0, 7.9, 1H), 4.92 (s, 1H), 4.66 (t, J=7.4, 1H), 3.71 (s, 3H), 3.63–3.51 (m, 1H), 3.51–3.39 (m, 1H), 2.63 (dd, J=13.0, 10.6, 1H), 2.24–2.08 (m, 2H), 1.99–1.78 ppm (m, 3H); ^{13}C NMR (101 MHz, DMSO) δ=174.44, 167.31, 166.21, 158.41, 158.34 (d, J=238.7), 137.12, 135.42 (d, J=8.2), 129.35, 127.34, 114.61 (d, J=23.9), 113.14, 111.21 (d, J=24.5), 110.20 (d, J=8.2), 68.04, 60.47, 58.69, 56.85, 54.93, 44.86, 33.05, 26.84, 23.39 ppm; FTIR: $\tilde{\nu}$=3321, 2936, 2894, 1729, 1647, 1611, 1511, 1485, 1455, 1427, 1302, 1285, 1243, 1224, 1172, 1137, 1031 cm^{-1}; HRMS: calcd for $[M+H]^+$ $C_{24}H_{23}O_4N_3F$: 436.16671, found: 436.16626; $[\alpha]_D^{RT}$ −270.5 (DMSO, c 0.5).

*4.2.15. (2R,3S,5aS,10aS)-5′-Fluoro-3-phenyl-5a,6,7,8-tetrahydro-1H,5H-spiro[dipyrrolo[1,2-a:1′,2′-d]pyrazine-2,3′-indole]-2′,5,10(1′H,10aH)-trione (**11b**).* ^{1}H NMR (500 MHz, DMSO) δ=10.40 (s, 1H), 7.53 (dd, J=8.7, 2.5 Hz, 1H), 7.26–7.18 (m, 3H), 7.12 (td, J=9.3, 2.5 Hz, 1H), 6.89–6.84 (m, 3H), 5.11 (dd, J=10.4, 7.7 Hz, 1H), 4.99 (s, 1H), 4.70 (t, J=7.5 Hz, 1H), 3.61 (dt, J=14.5, 7.2 Hz, 1H), 3.52–3.45 (m, 1H), 2.65 (dd, J=13.1, 10.4 Hz, 1H), 2.23 (dd, J=13.1, 7.7 Hz, 1H), 2.20–2.13 (m, 1H), 2.01–1.83 ppm (m, 3H); ^{13}C NMR (126 MHz, DMSO) δ=174.27, 167.33, 166.10, 158.30 (d, J=237.0 Hz), 137.29, 137.05, 135.35 (d, J=8.8 Hz), 127.69, 127.24, 114.61 (d, J=23.0 Hz), 111.18 (d, J=24.9 Hz), 110.19 (d, J=6.5 Hz), 68.39, 60.42, 58.74, 56.82, 44.81, 33.18, 26.78, 23.33 ppm; FTIR: $\tilde{\nu}$=3296, 2926, 2854, 1731, 1656, 1488, 1458, 1425, 1301, 1272, 1224, 1180, 1139, 1030, 977 cm^{-1}; HRMS: calcd for $[M+H]^+$ $C_{23}H_{20}FN_3O_3$: 406.15615, found: 406.15592; $[\alpha]_D^{RT}$ −158.50 (DMSO, c 1.00).

*4.2.16. (2R,3S,5aS,10aS)-3-(4-Bromophenyl)-5′-fluoro-5a,6,7,8-tetrahydro-1H,5H-spiro[dipyrrolo[1,2-a:1′,2′-d]pyrazine-2,3′-indole]-2′,5,10(1′H,10aH)-trione (**11c**).* ^{1}H NMR (500 MHz, DMSO) δ=10.43 (s, 1H), 7.53 (dd, J=8.5, 2.1 Hz, 1H), 7.42 (d, J=8.2 Hz, 2H), 7.14–7.08 (m, 1H), 6.90–6.79 (m, 3H), 5.09 (dd, J=10.1, 7.9 Hz, 1H), 5.01 (s, 1H), 4.68 (t, J=7.4 Hz, 1H), 3.64–3.56 (m, 1H), 3.51–3.43 (m, 1H), 2.61 (dd, J=13.1, 10.1 Hz, 1H), 2.25 (dd, J=13.1, 7.9 Hz, 1H), 2.21–2.13 (m, 1H), 2.05–1.83 ppm (m, 3H); ^{13}C NMR (126 MHz, DMSO) δ=174.39, 167.38, 165.95, 158.33 (d, J=236.3 Hz), 137.07, 136.84, 135.07 (d, J=8.3 Hz), 130.61, 129.61, 120.38, 114.70 (d, J=23.5 Hz), 111.25 (d, J=24.8 Hz), 110.28 (d, J=8.2 Hz), 67.60, 60.39, 58.78, 56.66, 44.81, 33.48, 26.80, 23.29 ppm; FTIR: $\tilde{\nu}$=3293, 2924, 2854, 1727, 1650, 1486, 1457, 1427, 1299, 1218, 1174, 1136, 1105, 1071, 1008 cm^{-1}; HRMS: calcd for $[M+H]^+$ $C_{23}H_{19}{}^{79}BrFN_3O_3$: 484.06666, found: 484.06546; HRMS: $C_{23}H_{19}{}^{81}BrFN_3O_3$: 486.06461, found: 486.06327; $[\alpha]_D^{RT}$ −143.33 (DMSO, c 0.63).

*4.2.17. (2R,3S,5aS,10aS)-6′-Bromo-3-(4-methoxyphenyl)-5a,6,7,8-tetrahydro-1H,5H-spiro[dipyrrolo[1,2-a:1′,2′-d]pyrazine-2,3′-indole]-2′,5,10(1′H,10aH)-trione (**11d**).* ^{1}H NMR (400 MHz, DMSO) δ=10.49 (s, 1H), 7.46 (d, J=8.0, 1H), 7.20 (dd, J=8.0, 1.8, 1H), 6.99 (d, J=1.8, 1H), 6.76 (s, 4H), 5.02 (dd, J=10.4, 7.5, 1H), 4.92 (s, 1H), 4.61 (t, J=7.3, 1H), 3.71 (s, 3H), 3.62–3.52 (m, 1H), 3.49–3.40 (m, 1H), 2.61 (dd, J=13.1, 10.5, 1H), 2.22–2.09 (m, 2H), 1.98–1.79 ppm (m, 3H); ^{13}C NMR (101 MHz, DMSO) δ=174.35, 167.19, 166.16, 158.42, 142.73, 133.21, 129.24, 127.39, 124.93, 124.27, 121.09, 113.15, 112.34, 67.94, 60.46, 58.78, 56.11, 54.93, 44.85, 33.05, 26.86, 23.38 ppm; FTIR: $\tilde{\nu}$=3252, 2923, 2851, 1733, 1655, 1610, 1512, 1482, 1448, 1418, 1326, 1303, 1245, 1210, 1174, 1117, 1035; $[\alpha]_D^{RT}$ −215.2 ($CHCl_3$, c 0.5).

4.2.18. (2R,3S,5aS,10aS)-6′-Bromo-3-(4-bromophenyl)-5a,6,7,8-tetrahydro-1H,5H-spiro[dipyrrolo[1,2-a:1′,2′-d]pyrazine-2,3′-indole]-

*2′,5,10(1′H,10aH)-trione (**11e**).* ^{1}H NMR (500 MHz, DMSO) δ=10.57 (s, 1H), 7.51 (d, J=8.0 Hz, 1H), 7.43 (d, J=8.6 Hz, 2H), 7.24 (dd, J=8.0, 1.8 Hz, 1H), 7.02 (d, J=1.8 Hz, 1H), 6.85 (d, J=6.5 Hz, 2H), 5.07 (dd, J=10.2, 7.7 Hz, 1H), 5.01 (s, 1H), 4.64 (t, J=7.4 Hz, 1H), 3.65–3.56 (m, 1H), 3.51–3.44 (m, 1H), 2.60 (dd, J=13.2, 10.2 Hz, 1H), 2.24 (dd, J=13.2, 7.7 Hz, 1H), 2.22–2.13 (m, 1H), 2.00–1.83 ppm (m, 3H); ^{13}C NMR (126 MHz, DMSO) δ=174.30, 167.26, 165.89, 142.68, 136.74, 132.87, 130.61, 124.96, 124.33, 121.17, 120.40, 112.39, 67.49, 60.36, 58.85, 55.94, 44.80, 33.46, 26.81, 23.27 ppm; FTIR: $\tilde{\nu}$=3064, 2926, 2852, 1723, 1650, 1611, 1483, 1452, 1409, 1328, 1301, 1273, 1261, 1216, 1155, 1117, 1069, 1025, 1008 cm^{-1}; HRMS: calcd for $[M+H]^+$ $C_{23}H_{19}{}^{79}Br_2N_3O_3$: 543.98659, found: 543.98625; HRMS: $C_{23}H_{19}{}^{81}Br_2N_3O_3$: 547.98250, found: 547.98191; $[\alpha]_D^{RT}$ −184.62 ($CHCl_3$, c 0.65).

*4.2.19. (2R,3S,5aS,10aS)-3-(4-Bromophenyl)-5a,6,7,8-tetrahydro-1H,5H-spiro[dipyrrolo[1,2-a:1′,2′-d]pyrazine-2,3′-indole]-2′,5,10(1′H,10aH)-trione (**11f**).* ^{1}H NMR (500 MHz, DMSO) δ=10.39 (s, 1H), 7.50 (d, J=7.4, 1H), 7.39 (d, J=8.4, 2H), 7.24 (t, J=7.7, 1H), 7.02 (dd, J=7.7, 7.4, 1H) 6.85 (d, J=7.7, 1H), 6.79 (d, J=8.4, 2H), 5.06 (dd, J=10.6, 8.1, 1H), 4.93 (s, 1H), 4.62 (t, J=7.5, 1H), 3.62–3.52 (m, 1H), 3.48–3.40 (m, 1H), 2.59 (dd, J=13.0, 10.6, 1H), 2.22–2.08 (m, 2H), 1.98–1.78 ppm (m, 3H); ^{13}C NMR (126 MHz, DMSO) δ=175.35, 168.22, 166.93, 141.70, 137.86, 134.56, 131.51, 129.46, 123.90, 122.87, 121.23, 110.52, 68.79, 61.27, 59.85, 57.01, 45.71, 34.55, 27.73, 24.19 ppm; FTIR: $\tilde{\nu}$=3254, 2946, 2887, 1724, 1652, 1617, 1486, 1470, 1429, 1334, 1294, 1212, 1149, 1105, 1073, 1008 cm^{-1}; HRMS: calcd for $[M+H]^+$ $C_{23}H_{20}{}^{79}BrN_3O_3$: 466.07608, found: 466.07583; HRMS: calcd for $[M+H]^+$ $C_{23}H_{20}{}^{81}BrN_3O_3$: 468.07403, found: 468.07365; $[\alpha]_D^{RT}$ −9.8 ($CHCl_3$, c 1.0).

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Supplementary data

Copies of ^{1}H NMR- and ^{13}C NMR-spectra and HPLC traces are provided. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2011.04.056.

References and notes

1. (a) Koehn, F. E.; Carter, G. T. *Nat. Rev. Drug Discovery* **2005**, *4*, 206–220; (b) Lam, K. S. *Trends Microbiol.* **2007**, *15*, 279–289; (c) Newman, D. J.; Cragg, G. M. *J. Nat. Prod.* **2007**, *70*, 461–477; (d) Ganesan, A. *Curr. Opin. Chem. Biol.* **2008**, *12*, 306–317; (e) Harvey, A. L. *Drug Discovery Today* **2008**, *13*, 894–901; (f) Li, J. W. H.; Vederas, J. C. *Science* **2009**, *325*, 161–165; (g) Molinski, T. F.; Dalisay, D. S.; Lievens, S. L.; Saludes, J. P. *Nat. Rev. Drug Discovery* **2009**, *8*, 69–85.
2. (a) Meseguer, B.; Alonso-Diaz, D.; Griebenow, N.; Herget, T.; Waldmann, H. *Angew. Chem., Int. Ed.* **1999**, *38*, 2902–2906; (b) Meseguer, B.; Alonso-Diaz, D.; Griebenow, N.; Herget, T.; Waldmann, H. *Chem.—Eur. J.* **2000**, *6*, 3943–3957; (c) Brohm, D.; Metzger, S.; Bhargava, A.; Muller, O.; Lieb, F.; Waldmann, H. *Angew. Chem., Int. Ed.* **2001**, *41*, 307–311; (d) Brohm, D.; Philippe, N.; Metzger, S.; Bhargava, A.; Muller, O.; Lieb, F.; Waldmann, H. *J. Am. Chem. Soc.* **2002**, *124*, 13171–13178; (e) Koch, M. A.; Wittenberg, L. O.; Basu, S.; Jeyaraj, D. A.; Gourzoulidou, E.; Reinecke, K.; Odermatt, A.; Waldmann, H. *Proc. Natl. Acad. Sci. U.S. A.* **2004**, *101*, 16721–16726; (f) Koch, M. A.; Schuffenhauer, A.; Scheck, M.; Wetzel, S.; Casaulta, M.; Odermatt, A.; Ertl, P.; Waldmann, H. *Proc. Natl. Acad. Sci. U.S.A.* **2005**, *102*, 17272–17277; (g) Nören-Müller, A.; Reis-Correa, I.; Prinz, H.; Rosenbaum, C.; Saxena, K.; Schwalbe, H. J.; Vestweber, D.; Cagna, G.; Schunk, S.; Schwarz, O.; Schiewe, H.; Waldmann, H. *Proc. Natl. Acad. Sci. U.S.A.* **2006**, *103*, 10606–10611; (h) Garcia, A. B.; Lessmann, T.; Umarye, J. D.; Mamane, V.; Sommer, S.; Waldmann, H. *Chem. Commun.* **2006**, 3868–3870; (i) Schuffenhauer, A.; Ertl, P.; Roggo, S.; Wetzel, S.; Koch, M. A.; Waldmann, H. *J. Chem. Inf. Model.* **2007**, *47*, 47–58; (j) Kaiser, M.; Wetzel, S.; Kumar, K.; Waldmann, H. *Cell. Mol. Life Sci.* **2008**, *65*, 1186–1201; (k) Waldmann, H.; Khedkar, V.; Dückert, H.; Schürmann, M.; Oppel, I. M.; Kumar, K. *Angew. Chem., Int. Ed.* **2008**, *47*, 6869–6872; (l) Nören-Müller, A.; Wilk, W.; Saxena, K.; Schwalbe, H.; Kaiser, M.; Waldmann, H. *Angew. Chem., Int. Ed.* **2008**, *47*, 5973–5977; (m) Kumar, K.; Waldmann, H. *Angew. Chem., Int. Ed.* **2009**, *48*, 3224–3242; Renner, S.; van Otterlo, W. A. L.; Seoane, M. D.; Mocklinghoff, S.; Hofmann, B.; Wetzel, S.; Schuffenhauer, A.; Ertl, P.; Oprea, T. I.; Steinhilber, D.; Brunsveld, L.; Rauh, D.; Waldmann, H. *Nat. Chem. Biol.* **2009**, *5*, 585–592; (n) Wetzel, S.; Klein, K.; Renner, S.; Rauh, D.; Oprea, T. I.; Mutzel, P.; Waldmann, H. *Nat. Chem. Biol.* **2009**, *5*, 581–583; (o) Wetzel, S.; Wilk, W.; Chammaa, S.; Sperl, B.; Roth, A. G.; Yektaoglu, A.; Renner, S.; Berg, T.; Arenz, C.; Giannis, A.; Oprea, T. I.; Rauh, D.; Kaiser, M.; Waldmann, H. *Angew. Chem., Int. Ed.* **2010**, *49*, 3666–3670; (p) Dekker, F. J.; Rocks, O.; Vartak, N.; Menninger, S.; Hedberg, C.; Balamurugan, R.; Wetzel, S.; Renner, S.; Gerauer, M.; Scholermann, B.; Rusch, M.; Kramer, J. W.; Rauh, D.; Coates, G. W.; Brunsveld, L.; Bastiaens, P. I. H.; Waldmann, H. *Nat. Chem. Biol.* **2010**, *6*, 449–456; (q) Bon, R. S.; Waldmann, H. *Acc. Chem. Res.* **2010**, *43*, 1103–1114; (r) Basu, S.; Ellinger, B.; Rizzo, S.; Deraeve, C.; Schürmann, M.; Preut, H.; Arndt, H.-D.; Waldmann, H. *Proc. Natl. Acad. Sci. U.S.A.* **2011**, *108*, 6805–6810.
3. (a) Bindra, J. S. In *The Alkaloids*; Manske, R. H. F., Ed.; Academic: New York, 1973; Vol. 14, pp 84–121; (b) Sakai, S.; Aimi, N.; Yamaguchi, K.; Ohhira, H.; Hori, K.; Haginiwa, J. *Tetrahedron Lett.* **1975**, *16*, 715–718; (c) Aimi, N.; Yamaguchi, K.; Sakai, S.; Haginiwa, J.; Kubo, A. *Chem. Pharm. Bull.* **1978**, *26*, 3444–3449; (d) Sakai, S.; Aimi, N.; Yamaguchi, K.; Yamanaka, E.; Haginiwa, J. *J. Chem. Soc., Perkin Trans. 1* **1982**, 1257–1262; (e) Wong, W. H.; Lim, P. B.; Chuah, C. H. *Phytochemistry* **1996**, *41*, 313–315; (f) Pellegrini, C.; Weber, M.; Borschberg, H. J. *Helv. Chim. Acta* **1996**, *79*, 151–168; (g) Anderton, N.; Cockrum, P. A.; Colegate, S. M.; Edgar, J. A.; Flower, K.; Vit, I.; Willing, R. I. *Phytochemistry* **1998**, *48*, 437–439; (h) Reyes-Chilpa, R.; Rivera, J.; Oropeza, M.; Mendoza, P.; Amekraz, B.; Jankowski, C.; Campos, M. *Biol. Pharm. Bull.* **2004**, *27*, 1617–1620; (i) Kam, T. S.; Choo, Y. M. *Tetrahedron* **2000**, *56*, 6143–6150; (j) Ma, J.; Hecht, S. M. *Chem. Commun.* **2004**, 1190–1191; (k) Pandey, R.; Singh, S. C.; Gupta, M. M. *Phytochemistry* **2006**, *67*, 2164–2169.
4. (a) Cui, C. B.; Kakeya, H.; Osada, H. *Tetrahedron* **1996**, *52*, 12651–12666; (b) Cui, C. B.; Kakeya, H.; Osada, H. *J. Antibiot.* **1996**, *49*, 832–835; (c) Wang, F. Z.; Fang, Y. C.; Zhu, T. J.; Zhang, M.; Lin, A. Q.; Gu, Q. Q.; Zhu, W. M. *Tetrahedron* **2008**, *64*, 7986–7991.
5. Edmondson, S.; Danishefsky, S. J.; Sepp-Lorenzino, L.; Rosen, N. *J. Am. Chem. Soc.* **1999**, *121*, 2147–2155.
6. Antonchick, A. P.; Gerding-Reimers, C.; Catarinella, M.; Schürmann, M.; Preut, H.; Ziegler, S.; Rauh, D.; Waldmann, H. *Nat. Chem.* **2010**, *2*, 735–740.
7. For a review on the challenge of developing catalytic asymmetric methods for the synthesis of quaternary all-carbon centers, see: (a) Corey, E. J.; Guzman-Perez, A. *Angew. Chem., Int. Ed.* **1998**, *37*, 388–401; (b) Douglas, C. J.; Overman, L. E. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5363–5367; (c) Trost, B. M.; Jiang, C. H. *Synthesis* **2006**, 369–396; (d) Cozzi, P. G.; Hilgraf, R.; Zimmermann, N. *Eur. J. Org. Chem.* **2007**, 5969–5994; (e) Steven, A.; Overman, L. E. *Angew. Chem., Int. Ed.* **2007**, *46*, 5488–5508; (f) Trost, B. M.; Brennan, M. K. *Synthesis* **2009**, 3003–3025.
8. For excellent reviews on the synthesis of 3,3′-pyrrolidinyl-spirooxindoles, see: (a) Marti, C.; Carreira, E. M. *Eur. J. Org. Chem.* **2003**, 2209–2219; (b) Galliford, C. V.; Scheidt, K. A. *Angew. Chem., Int. Ed.* **2007**, *46*, 8748–8758.
9. (a) Edmondson, S. D.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **1998**, *37*, 1138–1140; (b) Ito, M.; Clark, C. W.; Mortimore, M.; Goh, J. B.; Martin, S. F. *J. Am. Chem. Soc.* **2001**, *123*, 8003–8010; (c) Wearing, X. Z.; Cook, J. M. *Org. Lett.* **2002**, *4*, 4237–4240; (d) Takayama, H.; Fujiwara, R.; Kasai, Y.; Kitajima, M.; Aimi, N. *Org. Lett.* **2003**, *5*, 2967–2970; (e) Li, C. M.; Chan, C.; Heimann, A. C.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2007**, *46*, 1444–1447.
10. (a) von Nussbaum, F.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2000**, *39*, 2175–2178; (b) Miyake, F. Y.; Yakushijin, K.; Horne, D. A. *Angew. Chem., Int. Ed.* **2004**, *43*, 5357–5360.
11. (a) Sebahar, P. R.; Williams, R. M. *J. Am. Chem. Soc.* **2000**, *122*, 5666–5667; (b) Sebahar, P. R.; Osada, H.; Usui, T.; Williams, R. M. *Tetrahedron* **2002**, *58*, 6311–6322; (c) Onishi, T.; Sebahar, P. R.; Williams, R. M. *Org. Lett.* **2003**, *5*, 3135–3137; (d) Lo, M. M. C.; Neumann, C. S.; Nagayama, S.; Perlstein, E. O.; Schreiber, S. L. *J. Am. Chem. Soc.* **2004**, *126*, 16077–16086; (e) Galliford, C. V.; Martenson, J. S.; Stern, C.; Scheidt, K. A. *Chem. Commun.* **2007**, 631–633.
12. Malinakova, H. C.; Liebeskind, L. S. *Org. Lett.* **2000**, *2*, 4083–4086.
13. Overman, L. E.; Rosen, M. D. *Angew. Chem., Int. Ed.* **2000**, *39*, 4596–4599.
14. (a) Lakshmaiah, G.; Kawabata, T.; Shang, M. H.; Fuji, K. *J. Org. Chem.* **1999**, *64*, 1699–1704; (b) Bagul, T. D.; Lakshmaiah, G.; Kawabata, T.; Fuji, K. *Org. Lett.* **2002**, *4*, 249–251.
15. (a) Alper, P. B.; Meyers, C.; Lerchner, A.; Siegel, D. R.; Carreira. *Angew. Chem., Int. Ed.* **1999**, *38*, 3186–3189; (b) Lerchner, A.; Carreira, E. M. *J. Am. Chem. Soc.* **2002**, *124*, 14826–14827; (c) Meyers, C.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2003**, *42*, 694–696; (d) Marti, C.; Carreira, E. M. *J. Am. Chem. Soc.* **2005**, *127*, 11505–11515.
16. Trost, B. M.; Stiles, D. T. *Org. Lett.* **2007**, *9*, 2763–2766.
17. For recent reviews on asymmetric [3+2] cycloaddition of azomethine ylides, see: (a) Najera, C.; Sansano, J. M. *Angew. Chem., Int. Ed.* **2005**, *44*, 6272–6276; (b) Pandey, G.; Banerjee, P.; Gadre, S. R. *Chem. Rev.* **2006**, *106*, 4484–4517; (c) Pellissier. *Tetrahedron* **2007**, *63*, 3235–3285; (d) Naodovic, M.; Yamamoto, H. *Chem. Rev.* **2008**, *108*, 3132–3148; (e) Patil, N. T.; Yamamoto, Y. *Chem. Rev.* **2008**, *108*, 3395–3442; (f) Stanley, L. M.; Sibi, M. P. *Chem. Rev.* **2008**, *108*, 2887–2902.
18. For recent results on asymmetric [3+2] cycloaddition of azomethine ylides, see: (a) Chen, X. H.; Zhang, W. Q.; Gong, L. Z. *J. Am. Chem. Soc.* **2008**, *130*, 5652–5653; (b) Fukuzawa, S. I.; Oki, H. *Org. Lett.* **2008**, *10*, 1747–1750; (c) Lopez-Perez, A.; Adrio, J.; Carretero, J. C. *J. Am. Chem. Soc.* **2008**, *130*, 10084–10085; (d) Najera, C.; Retamosa, M. D.; Sansano, J. M. *Angew. Chem., Int. Ed.* **2008**, *47*, 6055–6058; (e)

Wang, C. J.; Liang, G.; Xue, Z. Y.; Gao, F. *J. Am. Chem. Soc.* **2008**, *130*, 17250–17251; (f) Hernandez-Toribio, J.; Arrayas, R. G.; Martin-Matute, B.; Carretero, J. C. *Org. Lett.* **2009**, *11*, 393–396; (g) Lopez-Perez, A.; Adrio, J.; Carretero, A. C. *Angew. Chem., Int. Ed.* **2009**, *48*, 340–343; (h) Chen, X. H.; Wei, Q.; Luo, S. W.; Xiao, H.; Gong, L. Z. *J. Am. Chem. Soc.* **2009**, *131*, 13819–13825; (i) Arai, T.; Mishiro, A.; Yokoyama, N.; Suzuki, K.; Sato, H. *J. Am. Chem. Soc.* **2010**, *132*, 5338–5339.

19. Up to date only a few examples are reported, with methacrolein (a) Cabrera, S.; Arrayas, R. G.; Carretero, J. C. *J. Am. Chem. Soc.* **2005**, *127*, 16394–16395 And with methyl methacrylate: (b) Kim, H. Y.; Shih, H. J.; Knabe, W. E.; Oh, K. *Angew. Chem., Int. Ed.* **2009**, *48*, 7420–7423.
20. (a) Wenkert, E.; Udelhofen, J. H.; Bhattacharyya, N. K. *J. Am. Chem. Soc.* **1959**, *81*, 3763–3768; (b) Seaton, J. C.; Nair, M. D.; Edwards, O. E.; Marion, L. *Can. J. Chem.* **1960**, *38*, 1035–1042.
21. Additionally, different bases, Cu(I), Cu(II) and Ag(I) salts were tested in the 1,3-dipolar cycloaddition under optimized reaction conditions but did not give better results.