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Enantioselective Construction of Spirocyclic Oxindoles via Tandem Michael/Michael Reactions Catalyzed by Multifunctional Quaternary Phosphonium Salt

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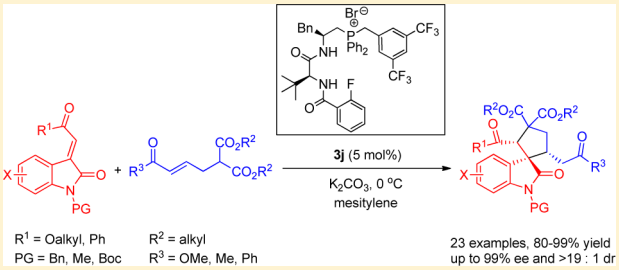
Supporting Information

ABSTRACT: The enantioselective construction of five-membered spirocyclic oxindoles via a double Michael cascade reaction is described by using dipeptide-based multifunctional quaternary phosphonium salt catalysts. The desired products were obtained in excellent yields (up to 94%) and good to high stereoselectivities (up to >19:1 dr and 99% ee).



The spirocyclic oxindole scaffold, which represents a privileged heterocyclic motif, has been widely featured in alkaloids and pharmacologically interesting compounds (Figure 1).[1] Owing to the diverse bioactivities and structural

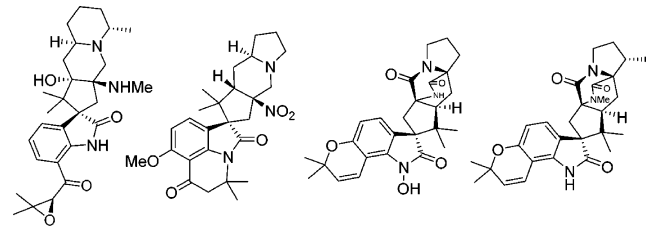


Figure 1. Examples of natural products containing the spirocyclopentane oxindole scaffold.

complexity of five-membered spirocyclic oxindoles, various approaches for synthesizing these molecules have been reported in the past few years.[2] Since Trost and co-workers reported a palladium-catalyzed [3+2] cycloaddition for the preparation of five-membered spirocyclic oxindoles in 2007,[3] many efficient strategies have been developed that involve transition-metal catalysis and organocatalysis.[4] In the case of organocatalytic reactions, these have mainly focused on using chiral phosphine[5] or amine catalysts,[6] hydrogen-bonding catalysts[7] or NHC catalysts.[8] The phase transfer catalysis which has evolved into a powerful and versatile methodology has been exploited to a lesser degree for the asymmetric synthesis of spirocyclic oxindole scaffolds.[9]

Inspired by our experience in the development of chiral organocatalysts derived from chiral amino acids for a range of asymmetric transformations,[10] we have reported amino-acid-derived bifunctional quaternary ammonium and phosphonium salts as chiral PTCs[11] in asymmetric aza-Henry,[12c,d] sulfa-Mannich reactions.[12e] Recently, we have developed asymmetric Michael/S_N2 tandem reaction to construction chiral five- and six-membered cyclic compounds (Scheme 1a)[12a] and Michael–Michael reaction to synthesis of functionalized cyclopentane (Scheme 1b)[12b] by using chiral dipeptide-derived phosphonium salt catalysts.

As part of our ongoing project on extending the application scope of these phase-transfer catalysts, we envisioned that chiral five-membered spirocyclic oxindoles could also be constructed via double Michael cascade reaction in a similar method. So far as we know, malonate-substituted α,β-unsaturated esters which have weak acidity and steric hindrance used in asymmetric cycloaddition reactions as nucleophiles are still limited.[13] Furthermore, the reaction between methyleneindolinones and malonate-substituted α,β-unsaturated esters to afford novel spirocyclicoxindole scaffolds have not yet been studied. Herein, we disclosed the application of the dipeptide-derived multifunctional quaternary phosphnium salts (Figure 2) to catalyze asymmetric Michael/Michael reaction to constructed chiral spriocyclicoxindoles.

Our initial investigations commenced with a model reaction of the *N*-benzyl protected methyleneindolinone **1a** and γ-

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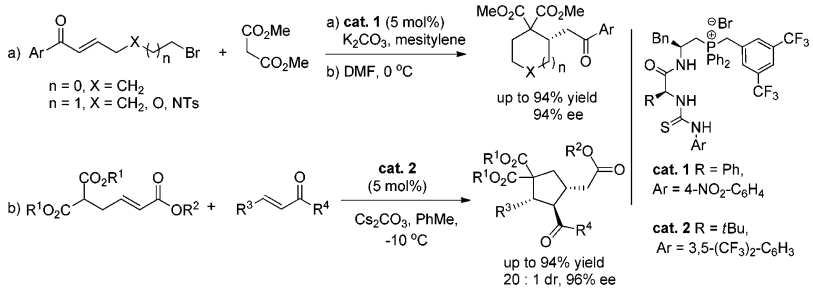
Scheme 1. Asymmetric Cascade Reaction Catalyzed by Chiral Dipeptide-Derived Phosphonium Salt Catalysts



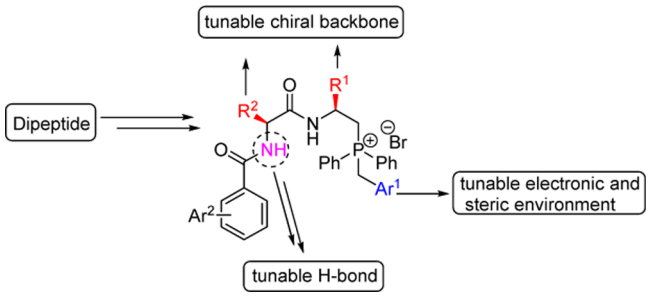


Figure 2. Rational design of dipeptide-derived multifunctional quaternary phosphonium.

malonate-substituted α,β-unsaturated ester **2a** catalyzed by a series of single chiral amino-acid-derived bifunctional phosphonium salts **3a**−**3d**. As indicated in Table 1, the reactions catalyzed by these phosphonium catalysts gave the desired product **4aa** in excellent yields (>96%) but only with moderate ee values. Relatively higher enantioselectivity and diastereoselectivity were observed by using L-phenylalanine-derived catalyst **3d** (entries 1−4). To improve the selectivities, additional dipeptide-based multifunctional phosphonium salts **3e**−**3j** were synthesized from L-phenylalanine and one other amino acid. The thiourea-type phosphonium catalyst **3e**, which has shown superior selectivity control in our previous reactions,[12] improved the enantioselectivity to 81% ee (entry 5). Catalyst **3h** with double amide N−H bond derived from L-phenylalanine and L-*tert*-butyl leucine, further improved the enantioselectivity to 90% ee (entry 8). Noteworthy, the two stereogenic centers and the structure of two amino acids in the catalyst have obvious influence on the stereochemical outcome of the reaction. The inferior results were obtained with catalyst **3f** with one of the chiral centers removed and catalyst **3i** derived from L-phenylalanine and D-*tert*-butyl leucine (entries 6 and 9, more details see the Supporting Information). Further optimization of the substitutions of the amide moiety furnished the optimum catalyst **3j**, with which the desired product **4aa** was obtained in 92% ee and 11:1 dr (entry 10, more details see the Supporting Information). Solvent and base screening revealed the reaction was preferably conducted in mesitylene with K_2CO_3 (entries 11−20). The absolute configuration of the major product **4aa** was assigned by analogy with **4ea**. The relative stereochemistry of the minor product **4aa′** has been determined through the NOE experiment (see the Supporting Information). Herein we got the optimized reaction conditions as a combination of K_2CO_3 (2 equiv) as a base, 5 mol% of catalyst **3j** and mesitylene as a solvent (entry 15).

Having identified the optimal reaction conditions, we then started to explore the generality of this protocol. First, various substituents on the aryl ring of the methyleneindolinones were evaluated in the reaction with **2a** (Table 2). All the reactions gave the desired products with high yields (>82%) and good selectivities (up to 99% ee and >19:1 dr). Both electron-donating and electron-withdrawing substituents in different positions were well tolerated (entries 1−14). The enantioselectivity could be further improved by a simple recrystallization from CH_2Cl_2 and hexanes (entry 4). The absolute configuration of **4ea** was determined by X-ray crystallographic analysis (see the Supporting Information) and the other products were assigned by analogy under the optimal reaction conditions.

Next, we set out to investigate the substrate scope related to different reaction pairs between methylenenindolinones and γ-malonate-substituted α,β-unsaturated compounds (Scheme 2). In general, all the reactions proceeded very smoothly to give the products in very high yields. Different α,β-unsaturated esters and α,β-unsaturated ketones were well tolerated and the corresponding cyclization products (**4ab**−**4ae**) were obtained in good to high stereoselectivity. Reaction with dimethyl malonate substituted α,β-unsaturated ester (R^3 = Me) gave the product **4ab** with a relatively lower ee (82%), while with *N*-Boc and *N*-methyl protected methyleneindolinones afforded the products (**4qa**−**4sa**) in satisfactory results. We also tried the *N*-acetyl protected, the phenyl, and cyano substituted methyleneindolinones, and the products were obtained with poor enantioselectivities (**4ta**−**4wa**). Six-membered spirocyclic oxindole could also be generated by using 1,1-diethyl 5-methyl (*E*)-pent-4-ene-1,1,5-tricarboxylate with **1a**, unfortunately, the target product was obtained in 60% yield and 38% ee (**4af**).

In order to get more insight into the dipeptide-derived catalytic system, control experiments were performed with two variants of the catalyst **3h** under the optimized reaction conditions. First, in the presence of 2 equiv of K_2CO_3 and 5 mol% of **3h**, we successfully isolated the product **4aa** in 99% yield with 90% ee and 15:1 dr in mesitylene. Then use of catalyst **3k** with a blocked hydrogen bonding site or catalyst **3l** without the quaternary phosphonium center led to inferior results in terms of yield, enantioselectivity, and reaction time compared to the catalyst **3h** (Scheme 3a). This result indicates the importance of the synergistic interaction of these two functionalities in the catalytic process.

Based on the above experimental results, a plausible transition-state model TS is proposed to explain the stereochemical results of the reaction. We proposed that the malonate carbanion of the nucleophile **2a** would be directed by the phosphonium center and one of the amide N−H of the catalyst **3j** through static electronic interaction and H-bonding interaction. At the meantime, the other amide N−H of the catalyst **3j** might activate the electrophilic methyleneindolinone **1a** on the ester carbonyl group. This assumption is supported

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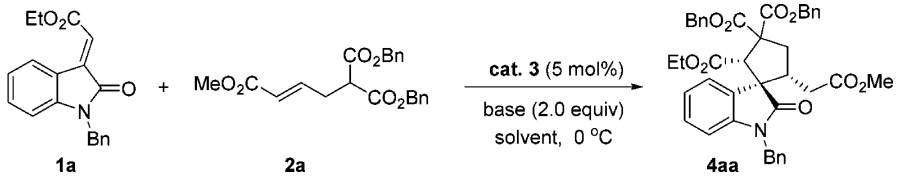
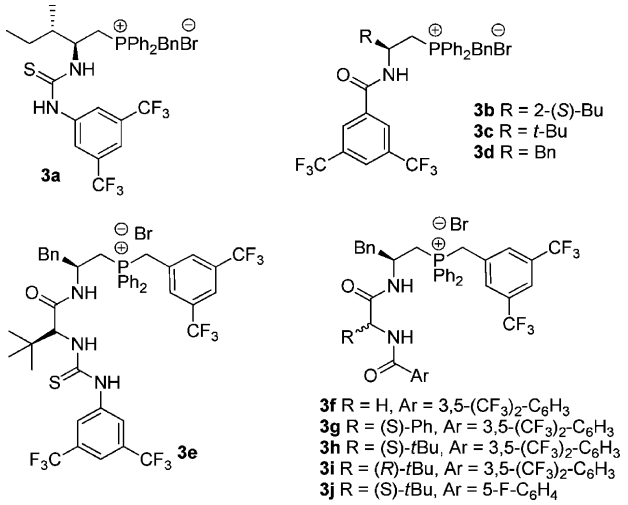
Table 1. Optimization of Reaction Conditions[a]



entry	cat.[h]	solvent	base	t (h)	yield [%][b]	dr[c]	ee [%][d]
1	**3a**	toluene	K_2CO_3	8	98	> 19:1	41[e]
2	**3b**	toluene	K_2CO_3	8	98	6:1	69(72)
3	**3c**	toluene	K_2CO_3	8	98	4:1	69(80)
4	**3d**	toluene	K_2CO_3	8	96	10:1	71(44)
5	**3e**	toluene	K_2CO_3	8	99	> 19:1	81
6	**3f**	toluene	K_2CO_3	8	98	> 19:1	3
7	**3g**	toluene	K_2CO_3	12	95	12:1	53
8	**3h**	toluene	K_2CO_3	8	99	15:1	90
9	**3i**	toluene	K_2CO_3	8	92	> 19:1	50[e]
10	**3j**	toluene	K_2CO_3	8	96	11:1	92
11	**3j**	CH_2Cl_2	K_2CO_3	32	90	> 19:1	84
12	**3j**	$CHCl_3$	K_2CO_3	32	77	9:1	75(73)
13	**3j**	Et_2O	K_2CO_3	7	90	8:1	88(80)
14	**3j**	$PhCF_3$	K_2CO_3	3	96	5:1	82(83)
15	**3j**	mestilyene	K_2CO_3	7	98	15:1	94
16	**3j**	mestilyene	KOH	4	98	5:1	0
17	**3j**	mestilyene	Cs_2CO_3	4	98	5:1	91(96)
18	**3j**	mestilyene	KF	48	96	6:1	92(96)
19[f]	**3j**	mestilyene	K_2CO_3	4	98	12:1	89
20[g]	**3j**	mestilyene	Cs_2CO_3	14	96	13:1	94

[a]Reaction conditions: **1a** (0.06 mmol), **2a** (0.09 mmol), and base (0.12 mmol) in the presence of catalyst **3** (5 mol%) in solvent (1.0 mL). [b]Isolated yields. [c]Determined by ^{1}H NMR analysis of the crude products. [d]ee of the major diastereomers was determined by chiral HPLC. The data in parentheses was the ee of the minor diastereomers. [e]Contrary configuration to **4aa**. [f]Reaction performed at rt. [g]Reaction performed at −10 °C. [h]



by the fact that when the ester is replaced by phenyl or cyano, the ee dropped dramatically. The steric hindrance drove the catalyst to control the incoming nucleophile attacking from *Re* face of methyleneindolinone (Scheme 3b). Removal of the protected Boc group could be achieved in the presence of trifluoroacetic acid and the product **5** was obtained with no loss of stereoselectivities (Scheme 3c).

In conclusion, we have developed a novel chiral quaternary phosphonium salt catalyzed asymmetric double Michael cascade reaction. This simple and efficient protocol offers a new method to access five-membered spirocyclicoxindole scaffolds from readily available substrates in excellent yields and good to high stereoselectivities.

EXPERIMENTAL SECTION

General Information. The melting points recorded are uncorrected. Nuclear magnetic resonance spectra were recorded at 400 MHz. All chemical shifts (δ) were given in ppm. Data were reported as follows: chemical shift, integration, multiplicity (s = single, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), and coupling constants (Hz). ee values were determined using an HPLC equipped with a PDA detector and a chiral column. Optical rotations were measured for solutions of samples of known concentrations in $CHCl_3$ or CH_2Cl_2 using a polarimeter equipped with a sodium vapor lamp. High-resolution mass spectra were recorded under TOF conditions. All solvents and reagents were directly used without further purification. Phase-transfer catalysts **3a**,[12c] **3b**−**3c**,[12e] **3d**,[12c] **3e**,[12b] and **3h**[12a] have been described, **3f**, **3g**, and **3i**−**3l** were prepared

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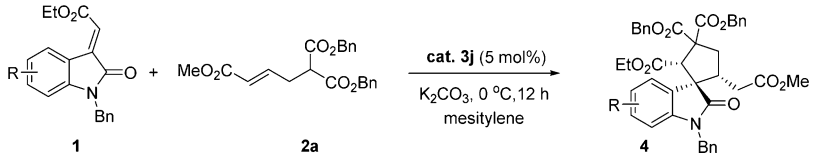
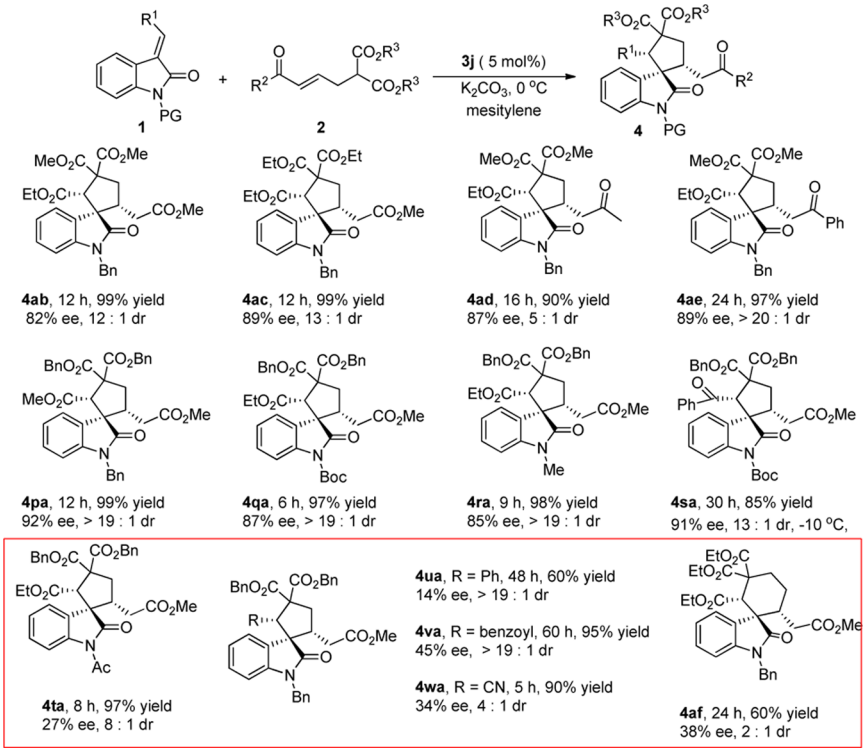
Table 2. Substrate Scope with Respect to the Substituted Methyleneindolinones[a]



entry	R	4	yield (%)[b]	dr[c]	ee (%)[d]
1	5-Cl	**4ba**	98	13:1	96
2	6-Cl	**4ca**	95	> 19:1	99
3	7-Cl	**4da**	97	> 19:1	88
4	5-F	**4ea**	90	16:1	90(98)[e]
5	6-F	**4fa**	98	12:1	94
6	7-F	**4ga**	96	> 19:1	90
7	5-CH_3	**4ha**	92	> 19:1	91
8	7-CH_3	**4ia**	80	> 19:1	92
9	5-OMe	**4ja**	97	12:1	94
10	6-OMe	**4ka**	90	> 19:1	92
11	5-OCF_3	**4la**	96	13:1	77
12	5-I	**4ma**	94	16:1	86
13	5-Br	**4na**	82	15:1	87
14	7-Br	**4oa**	97	11:1	82

[a]Reaction conditions: **1** (0.1 mmol), **2a** (0.15 mmol), and K_2CO_3 (0.2 mmol) in the presence of catalyst **3j** (5 mol%) in mesitylene (1.0 mL). [b]Isolated yields. [c]Determined by ^{1}H NMR analysis of the crude product. [d]The ee of major diastereomers determined by chiral HPLC. [e]The data in parentheses was achieved through recrystallization by using mixture of CH_2Cl_2 and hexanes.

Scheme 2. Substrate Scope with Respect to Methyleneindolinones and *α,β*-Unsaturated Compounds



following our reported literature.[12a,14] *γ*-Malonate-substituted *α,β*-unsaturated compounds were synthesized according to known procedure.[15]

*(S)-(2-(2-(3,5-Bis(trifluoromethyl)benzamido)acetamido)-3-phenylpropyl)(3,5-bis(trifluoromethyl)benzyl)diphenylphosphonium Bromide (**3f**).* 74 mg, yield 80%, white solid; mp =145−147 °C; $[\alpha]_D^{29.0}$ = +7.15 (*c* = 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) *δ* 9.34 (d, *J* = 8.8 Hz, 1H), 8.60 (t, *J* = 6.4 Hz, 1H), 8.35 (s, 2H), 7.79 (s, 1H), 7.66−7.75 (m, 2H), 7.41−7.58 (m, 9H), 7.28 (s, 2H), 7.11−7.20 (m, 3H), 6.98 (d, *J* = 6.8 Hz, 2H), 5.43 (t, *J* = 16.0 Hz, 1H), 4.85 (t, *J* = 14.4 Hz, 1H), 4.63−4.72 (m, 1H), 4.33−4.35 (m, 1H), 4.22 (dd, *J* = 16.4, 6.4 Hz, 1H), 3.65 (dd, *J* = 16.4, 6.4 Hz, 1H), 3.11−3.17 (m, 1H), 2.80 (dd, *J* = 13.2, 9.6 Hz, 1H), 2.53 (t, *J* = 10.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) *δ* 169.5, 164.5, 136.4, 135.5 (d, J_{C-P} = 2.9 Hz), 135.4 (d, J_{C-P} = 2.8 Hz), 134.8, 133.3 (2C), 133.2 (2C), 132.1, 131.9 (q, J_{C-F} = 33.7 Hz), 132.0 (d, J_{C-P} = 34.3 Hz), 131.1 (d, J_{C-P} = 12.4 Hz), 130.9 (d, J_{C-P} = 9.5 Hz), 130.4 (br. s), 131.8, 131.4, 131.1, 131.0, 130.9, 130.8 (br. s), 130.5 (d, J_{C-P} = 12.3 Hz), 130.3 (d, J_{C-P} = 12.4 Hz), 129.2, 128.7, 127.9, 127.3, 125.0 (br. s), 122.8 (q, J_{C-F} = 271.7

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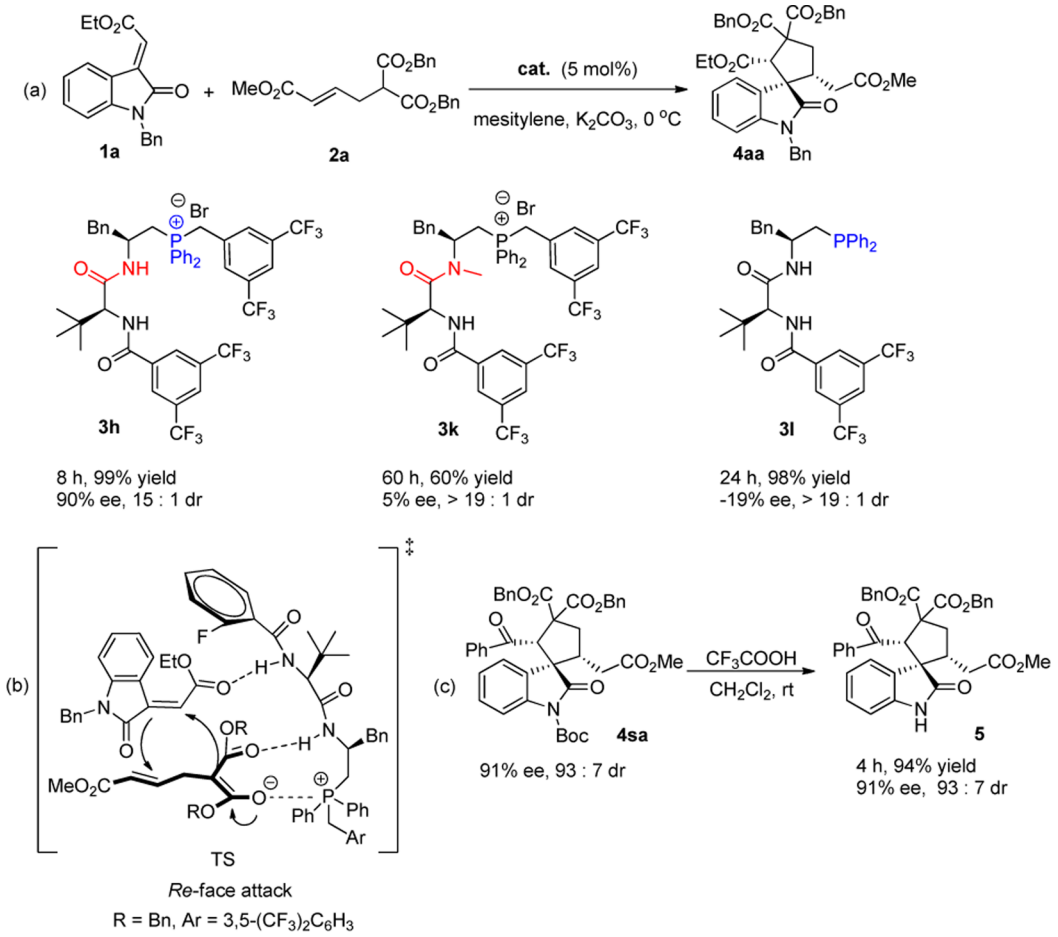
Scheme 3. Control Experiments, Proposed Transition State, and Simple Transformation of 4sa



Hz), 122.5 (q, J_{C-F} = 271.5 Hz), 121.9 (br. s), 117.2, 116.4, 115.0, 114.2, 46.2 (d, J_{C-P} = 4.6 Hz), 44.1, 43.1 (d, J_{C-P} = 4.6 Hz), 29.0 (d, J_{C-P} = 44.8 Hz), 26.5 (d, J_{C-P} = 48.9 Hz); ^{19}F NMR ($CDCl_3$, 376 MHz) δ −63.0, −63.4; ^{31}P NMR ($CDCl_3$, 162 MHz) δ 26.7; IR (Neat): 3199, 3057, 2927, 1658, 1543, 1439, 1374, 1279, 1177, 1135; HRMS (ESI): calcd for $[M\text{-}Br]^+$ $(C_{41}H_{32}F_{12}N_2O_2P)^+$ requires 843.2004; found 843.2010.

*((S)-2-((S)-2-(3,5-Bis(trifluoromethyl)benzamido)-2-phenylacetamido)-3-phenylpropyl) (3,5-bis(trifluoromethyl)benzyl) Diphenylphosphonium Bromide (**3g**).* 85 mg, yield 85%, white solid; mp =122−124 °C; $[\alpha]_D^{29.2}$ = +62.75 (c = 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.86−9.90 (m, 1H), 8.38 (d, J = 9.6 Hz, 2H), 8.21 (s, 1H), 7.89 (s, 1H), 7.75−7.79 (m, 3H), 7.61−7.67 (m, 4H), 7.46 (s, 2H), 7.29−7.40 (m, 6H), 7.12−7.22 (m, 4H), 7.01−7.06 (m, 4H), 5.81 (d, J = 6.4 Hz, 1H), 4.98−5.09 (m, 1H), 4.72−4.79 (m, 1H), 4.06−4.21 (m, 2H), 3.19−3.22 (m, 1H), 2.92−2.98 (m, 1H), 2.56−2.75 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.5, 163.9, 136.6, 136.5, 135.6 (d, J_{C-P} = 3.0 Hz), 135.4 (d, J_{C-P} = 2.8 Hz), 135.3, 135.2, 133.2, 133.1, 133.0, 132.9, 132.0 (d, J_{C-P} = 3.2 Hz), 131.6 (d, J_{C-P} = 3.0 Hz), 131.7 (q, J_{C-F} = 33.8 Hz), 130.7, 130.6, 130.5, 130.4, 130.3 (br. s), 130.2, 130.1, 129.2, 129.1, 128.7, 128.6, 128.0, 127.8, 126.9, 125.1 (br. s), 122.8 (q, J_{C-F} = 271.7 Hz), 122.3 (q, J_{C-F} = 271.6 Hz), 121.9 (br. s), 116.6, 115.8, 114.7, 113.8, 59.4, 47.2 (d, J_{C-P} = 4.7 Hz), 42.5 (d, J_{C-P} = 14.7 Hz), 28.9 (d, J_{C-P} = 44.6 Hz), 25.9 (d, J_{C-P} = 49.0 Hz); ^{19}F NMR ($CDCl_3$, 376 MHz) δ −62.9, −63.3; ^{31}P NMR ($CDCl_3$, 162 MHz) δ 27.0; IR (Neat): 3183, 3029, 2929, 1665, 1513, 1439, 1374, 1279, 1179, 1136; HRMS (ESI): calcd for $[M\text{-}Br]^+$ $(C_{47}H_{36}F_{12}N_2O_2P)^+$ requires 919.2306; found 919.2294.

*((S)-2-((S)-2-(3,5-Bis(trifluoromethyl)benzamido)-3,3-dimethylbutanamido)-3-phenylpropyl)(3,5-bis(trifluoromethyl)benzyl)-diphenylphosphonium Bromide (**3i**).* 88 mg, yield 90%, white solid; mp =120−122 °C; $[\alpha]_D^{29.0}$ = −12.20 (c = 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.48−9.51 (m, 1H), 8.30 (s, 2H), 8.08 (s, 1H), 7.76 (t, J = 7.2 Hz, 1H), 7.65−7.70 (m, 4H), 7.42−7.56 (m, 8H), 7.20−7.21 (m, 3H), 7.06−7.08 (m, 2H), 6.84 (s, 1H), 5.68−5.75 (m, 1H), 5.38−5.46 (m, 1H), 5.04−5.10 (m, 1H), 4.43 (d, J = 7.2 Hz, 1H), 4.25−4.27 (m, 1H), 3.24−3.27 (m, 1H), 2.92−2.98 (m, 1H), 2.72 (s, 1H), 2.50−2.57 (m, 1H), 1.18 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 169.9 165.0, 136.7, 136.2, 135.4 (d, J_{C-P} = 2.8 Hz), 135.3 (d, J_{C-P} = 2.8 Hz) 133.5, 133.4, 133.2, 133.1, 132.4 (q, J_{C-F} = 33.8 Hz), 131.9 (d, J_{C-P} = 3.1 Hz), 131.5 (d, J_{C-P} = 3.0 Hz), 131.4, 131.3, 130.9 (br. s), 130.3 (2C), 130.2, 130.1, 129.1, 129.0, 128.8, 127.2 (d, J_{C-P} = 2.6 Hz), 127.0, 125.3 (br. s), 122.8 (q, J_{C-F} = 271.6 Hz), 122.5 (q, J_{C-F} = 271.4 Hz), 121.7 (br. s), 116.9 (d, J_{C-P} = 84.4 Hz), 115.0, 114.2, 62.7, 46.9 (d, J_{C-P} = 4.3 Hz), 42.6 (d, J_{C-P} = 14.7 Hz), 33.8, 29.4 (d, J_{C-P} = 44.7 Hz), 27.2, 25.5 (d, J_{C-P} = 49.2 Hz); ^{19}F NMR ($CDCl_3$, 376 MHz) δ −63.1, −63.4; ^{31}P NMR ($CDCl_3$, 162 MHz) δ 27.5; IR (Neat): 3410, 3198, 3033, 2965, 1655, 1621, 1588, 1521, 1439, 1373, 1279, 1178, 1137; HRMS (ESI): calcd for $[M\text{-}Br]^+$ $(C_{45}H_{40}F_{12}N_2O_2P)^+$ requires 899.2630; found 899.2609.

*(3,5-Bis(trifluoromethyl)benzyl)((S)-2-((R)-2-(2-fluorobenzamido)-3,3-dimethylbutanamido)-3-phenylpropyl)diphenylphosphonium (**3j**).* 76 mg, yield 88%, white solid; mp =115−117 °C; $[\alpha]_D^{29.1}$ = +54.45 (c = 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.28 (s, 1H), 7.75−7.81 (m, 2H), 7.51−7.59 (m, 6H), 7.43 (t, J = 7.6 Hz, 1H), 7.32−7.35 (m, 4H), 7.23−7.26 (m, 1H), 7.16 (s, 2H), 7.00−7.05 (m, 4H), 6.92 (s, 2H), 6.65 (t, J = 7.6 Hz, 1H), 5.16 (t, J = 15.6 Hz, 1H), 4.94 (s, 1H), 4.79 (t, J = 14.4 Hz, 1H), 4.34 (d, J = 7.0 Hz, 1H), 4.24−4.29 (m, 1H), 3.14−3.17 (m, 1H), 2.86−2.92 (m, 1H), 2.25 (t, J = 14.4 Hz, 1H), 2.14−2.24 (m, 1H), 1.11 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.3, 164.5, 161.1 (d, J_{C-F} = 246.1 Hz), 136.9, 135.4 (d, J_{C-P} = 2.9 Hz), 135.0 (d, J_{C-P} = 2.9 Hz), 133.7 (d, J_{C-P} = 9.5 Hz), 133.2 (2C), 133.1 (2C), 132.2 (d, J_{C-P} = 3 Hz), 131.2 (d, J_{C-P} = 3 Hz), 131.9 (d, J_{C-P} = 3.3 Hz), 131.7 (d, J_{C-P} = 9.2 Hz), 131.6 (d, J_{C-P}

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= 3.3 Hz), 130.8, 130.7, 130.6, 129.9 (d, J_{C-P} = 12.3 Hz), 128.8 (d, J_{C-P} = 19.9 Hz), 126.8, 122.4 (q, J_{C-F} = 271.7 Hz), 123.6 (d, J_{C-P} = 3.2 Hz), 121.5 (br. s), 120.3 (d, J_{C-P} = 10.7 Hz), 117.1, 116.7, 116.4, 116.3, 115.1, 114.3, 64.7, 46.7 (d, J_{C-P} = 4.3 Hz), 42.4 (d, J_{C-P} = 15.1 Hz), 33.3, 28.0 (d, J_{C-P} = 43.6 Hz), 27.3, 23.5 (d, J_{C-P} = 49.1 Hz); ^{19}F NMR ($CDCl_3$, 376 MHz) δ −63.2, −109.6; ^{31}P NMR ($CDCl_3$, 162 MHz) δ 28.5; IR (Neat): 3435, 3191, 2964, 2870, 1656, 1518, 1480, 1439, 1373, 1279, 1177, 1138; HRMS (ESI): calcd for $[M-Br]^+$ $(C_{43}H_{41}F_7N_2O_2P)^+$ requires 781.2788; found 781.2772.

*((S)-2-((R)-2-(3,5-Bis(trifluoromethyl)benzamido)-N,3,3-trimethylbutanamido)-3-phenylpropyl)(3,5-bis(trifluoromethyl)benzyl)diphenylphosphonium Bromide (**3k**).* 79 mg, yield 80%, white solid; mp =121−123 °C; $[\alpha]_D^{28.4}$ = −7.61 (*c* = 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.15 (d, *J* = 12.0 Hz, 1H), 8.13 (d, *J* = 12.4 Hz, 1H), 8.01 (s, 2H), 8.00 (s, 1H), 7.68−7.83 (m, 6H), 7.53−7.58 (m, 3H), 7.32 (s, 2H), 6.81 (d, *J* = 7.2 Hz, 2H), 6.71 (d, *J* = 7.2 Hz, 2H), 6.54 (s, 1H), 6.43 (br, 1H), 5.78 (t, *J* = 15.2 Hz, 1H), 5.42 (t, *J* = 15.2 Hz, 1H), 5.01 (s, 1H), 4.70 (d, *J* = 9.2 Hz, 1H), 4.54 (td, *J* = 15.2, 5.6 Hz, 1H), 4.20 (td, J = 15.2, 5.6 Hz, 1H), 3.03 (s, 3H), 2.83−2.89 (m, 1H), 2.45 (d, *J* = 10.4 Hz, 1H), 0.81 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.9, 163.2, 135.9, 135.8, 135.6 (d, J_{C-P} = 2.4 Hz), 135.4 (d, J_{C-P} = 2.5 Hz), 134.5 (d, J_{C-P} = 9.6 Hz), 134.1 (q, J_{C-P} = 9.4 Hz), 132.1 (q, J_{C-F} = 33.6 Hz), 132.0 (d, J_{C-P} = 3.1 Hz), 131.7 (d, J_{C-P} = 3.3 Hz), 131.2 (d, J_{C-P} = 8.8 Hz), 131.1, 130.5 (d, J_{C-P} = 12.4 Hz), 130.3 (d, J_{C-P} = 12.3 Hz), 128.8, 128.1, 127.5 (d, J_{C-P} = 1.4 Hz), 126.6, 125.0, 122.9 (q, J_{C-F} = 271.3 Hz), 122.5 (q, J_{C-F} = 271.3 Hz), 121.8, 115.5, 115.3, 114.6, 114.5, 55.5, 39.9, 39.8, 35.9, 31.3, 30.8, 26.9, 26.5; ^{19}F NMR ($CDCl_3$, 376 MHz) δ −62.9, −63.2; ^{31}P NMR ($CDCl_3$, 162 MHz) δ 28.8; IR (Neat): 2963, 2869, 1624, 1482, 1466, 1374, 1279, 1178, 1136; HRMS (ESI): calcd for $[M-Br]^+$ $(C_{46}H_{42}F_{12}N_2O_2P)^+$ requires 913.2787; found 913.2788.

*N-((R)-1-(((S)-1-(diphenylphosphanyl)-3-phenylpropan-2-yl)amino)-3,3-dimethyl-1-oxobutan-2-yl)-3,5-bis(trifluoromethyl)benzamide (**3l**).* 65 mg, yield 87%, white solid; mp =56−58 °C; $[\alpha]_D^{28.5}$ = +18.33 (*c* = 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.11 (s, 2H), 7.95 (s, 1H), 7.21−7.32 (m, 9H), 7.18 (s, 1H), 7.06−7.09 (m, 2H), 6.97−7.01 (m, 3H), 6.87−6.91 (m, 1H), 5.91−5.97 (m, 1H), 4.28−4.32 (m, 1H), 4.15−4.20 (m, 1H), 2.81 (d, *J* = 6.4 Hz, 1H), 2.28 (ddd, *J* = 14.0, 5.2, 2.0 Hz, 1H), 2.14 (ddd, *J* = 8.8, 5.6, 2.8 Hz, 1H), 0.99 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 169.4, 164.2, 138.0, 137.4 (d, J_{C-P} = 11.6 Hz), 137.2 (d, J_{C-P} = 13.1 Hz), 136.3, 133.2, 132,9, 132.5, 132.3, 133.2 (q, J_{C-F} = 33.7 Hz), 129.4, 129.1, 128.7, 128.6, 128.5, 128.4, 127.4 (d, J_{C-P} = 3.6 Hz), 126.5, 125.2, 122.8 (q, J_{C-F} = 271.4 Hz), 61.5, 48.9 (d, J_{C-P} = 15.2 Hz), 41.8 (d, J_{C-P} = 7.8 Hz), 35.4, 33.6 (d, J_{C-P} = 15.2 Hz), 26.8 (d, J_{C-P} = 2.0 Hz); ^{19}F NMR ($CDCl_3$, 376 MHz) δ −62.8; ^{31}P NMR ($CDCl_3$, 162 MHz) δ −24.6; IR (Neat): 2963, 2869, 1624, 1482, 1466, 1374, 1279, 1178, 1136; HRMS (ESI): calcd for $[M + H]^+$ $(C_{36}H_{36}F_6N_2O_2P)^+$ requires 673.2413; found 673.2415.

General Procedure for the Michael/Michael Cascade Reaction. To a mixture of methyleneindolinones **1** (0.1 mmol, 1.0 equiv), catalyst **3j** (0.005 mmol, 0.05 equiv), and K_2CO_3 (0.2 mmol, 2.0 equiv) in mesitylene (1.0 mL) was added *α,β*-unsaturated compound **2** (0.12 mmol, 1.2 equiv) at 0 °C. The reaction was stirred at this temperature and monitored by TLC. After completion, the mixture was directly purified by column chromatography (petrolume ether/ethyl acetate = 5/1−3/1) on silica gel to afford the product.

*3,3-Dibenzyl-2-ethyl(1R,2S,5R)-1′-benzyl-5-(2-methoxy-2-oxoethyl)-2′-oxospiro[cyclopentane-1,3′-indoline]-2,3,3-tricarboxylate (**4aa**).* 68 mg, yield 98%; colorless oil; $[\alpha]_D^{28.2}$ = +5.67 (*c* = 1.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.45 (d, *J* = 7.6 Hz, 1H), 7.37−7.36 (m, 2H), 7.19−7.30 (m, 13H), 7.13 (t, *J* = 7.6 Hz, 1H), 6.90 (t, *J* = 7.6 Hz, 1H), 6.71 (d, *J* = 8.0 Hz, 1H), 5.14−5.27 (m, 3H), 5.01−5.08 (m, 2H), 4.87 (s, 1H), 4.72 (d, *J* = 15.6 Hz, 1H), 3.52−3.58 (m, 1H), 3.48 (s, 3H), 3.39−3.44 (m, 1H), 2.80−2.93 (m, 3H), 1.79−1.88 (m, 2H), 0.33 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 177.4, 171.3, 170.9, 169.8, 168.5, 143.2, 135.9, 135.3 (2C), 128.6, 128.5, 128.4, 128.3, 128.2 (2C), 127.8, 126.8, 125.7, 122.6, 108.9, 68.2, 67.9, 61.6, 60.7, 60.6, 57.7, 51.6, 44.4, 43.9, 41.0, 33.9, 13.0; IR (Neat): 3063, 3032, 2952, 1739, 1610, 1489, 1466, 1455, 1369, 1267, 1183; HRMS (ESI): calcd for $[M+H]^+$ $(C_{41}H_{40}O_9N)^+$ requires 690.2698; found 690.2691; enantiomeric excess: 94%, determined by HPLC (Chiralpak AD-H, hexane/*i*-PrOH 75/25, flow rate 1.0 mL/min; t_{major} = 28.5 min, t_{minor} = 52.6 min, λ = 254 nm).

*3,3-Dibenzyl-2-ethyl-1′-benzyl-5-(2-methoxy-2-oxoethyl)-2′-oxospiro[cyclopentane-1,3′-indoline]-2,3,3-tricarboxylate (**4aa′**).* 11 mg, yield 15%; colorless oil; $[\alpha]_D^{23.8}$ = −19.49 (*c* = 0.73, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.44 (d, *J* = 7.2 Hz, 1H), 7.26−7.35 (m, 15H), 7.14 (td, *J* = 7.6, 0.8 Hz, 1H), 6.98 (t, *J* = 8.0 Hz, 1H), 6.68 (d, *J* = 8.0 Hz, 1H), 5.38 (d, *J* = 12.4 Hz, 1H), 5.22 (d, *J* = 12.4 Hz, 1H), 5.14−5.18 (m, 3H), 4.73 (d, *J* = 15.6 Hz, 1H), 4.35 (s, 1H), 3.68−3.75 (m, 1H), 3.54−3.65 (m, 2H), 3.40 (s, 3H), 2.86 (dd, *J* = 13.6, 6.4 Hz, 1H), 2.40−2.53 (m, 2H), 2.16 (dd, *J* = 15.2, 6.0 Hz, 1H), 0.51 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 178.5, 171.7, 170.8, 170.4, 169.1, 143.0, 135.6, 135.4, 135.3, 129.5, 128.7, 128.6, 128.5 (3C), 128.3, 128.2 (2C), 128.1 (2C), 127.7, 127.4, 125.2, 123.1, 108.6, 67.7, 67.6, 61.6, 60.7, 59.1, 58.5, 51.5, 45.4, 43.9, 39.5, 34.4, 13.2; IR (Neat): 2953, 2925, 2854, 1737, 1709, 1611, 1489, 1467, 1454, 1370, 1238, 1177; HRMS (ESI): calcd for $[M+H]^+$ $(C_{41}H_{40}O_9N)^+$ requires 690.2698; found 690.2691; enantiomeric excess: 96%, determined by HPLC (Chiralpak AD-H, hexane/*i*-PrOH 75/25, flow rate 1.0 mL/min; t_{major} = 28.1 min, t_{minor} = 52.6 min, λ = 254 nm).

*3,3-Dibenzyl-2-ethyl-(1R,2S,5R)-1′-benzyl-5′-chloro-5-(2-methoxy-2-oxoethyl)-2′-oxospiro[cyclopentane-1,3′-indoline]-2,3,3-tricarboxylate (**4ba**).* 71 mg, yield 98%; colorless oil; $[\alpha]_D^{27.1}$ = +14.69 (*c* = 2.70, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.55 (d, *J* = 2.0 Hz, 1H), 7.19−7.33 (m, 15H), 7.13 (dd, *J* = 8.0, 2.0 Hz, 1H), 6.64 (d, *J* = 8.4 Hz, 1H), 5.21−5.26 (m, 2H), 5.15 (d, *J* = 12.4 Hz, 1H), 5.05−5.09 (m, 2H), 4.81 (s, 1H), 4.68 (d, *J* = 15.6 Hz, 1H), 3.62−3.66 (m, 1H), 3.49 (s, 3H), 3.42−3.46 (m, 1H), 2.94−2.99 (m, 1H), 2.73−2.87 (m, 2H), 1.87 (d, *J* = 6.8 Hz, 2H), 0.42 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 177.0, 171.1, 170.8, 169.8, 168.2, 141.9, 135.5, 135.2, 128.8, 128.7 (2C), 128.5 (2C), 128.3, 128.2 (2C), 128.0 (2C), 127.7, 126.0, 109.9, 68.3, 68.0, 61.1, 60.8, 60.6, 58.0, 51.7, 44.5, 44.1, 41.1, 33.9, 13.2; IR (Neat): 3064, 3032, 2951, 1739, 1609, 1485, 1455, 1433, 1344, 1267, 1177; HRMS (ESI): calcd for $[M+H]^+$ $(C_{41}H_{39}O_9NCl)^+$ requires 724.2308; found 724.2297; enantiomeric excess: 96%, determined by HPLC (Chiralpak AD-H, hexane/*i*-PrOH 75/25, flow rate 1.0 mL/min; t_{major} = 32.8 min, t_{minor} = 18.3 min, λ = 254 nm).

*3,3-Dibenzyl-2-ethyl-(1R,2S,5R)-1′-benzyl-6′-chloro-5-(2-methoxy-2-oxoethyl)-2′-oxospiro[cyclopentane-1,3′-indoline]-2,3,3-tricarboxylate (**4ca**).* 69 mg, yield 95%; colorless oil; $[\alpha]_D^{26.2}$ = −4.17 (*c* = 3.20, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.40 (d, *J* = 8.0 Hz, 1H), 7.23−7.34 (m, 13H), 7.18−7.20 (m, 2H), 6.87 (dd, *J* = 8.0, 1.2 Hz, 1H), 6.71 (d, *J* = 1.6 Hz, 1H), 5.14−5.25 (m, 3H), 5.01−5.05 (m, 2H), 4.82 (s, 1H), 4.67 (d, *J* = 15.2 Hz, 1H), 3.56−3.62 (m, 1H), 3.48 (s, 3H), 3.38−3.47 (m, 1H), 2.77−2.94 (m, 3H), 1.82−1.84 (m, 2H), 0.42 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 177.4, 171.1, 170.8, 169.9, 168.3, 144.5, 135.4, 135.2, 134.6, 128.9, 128.5 (2C), 128.3 (2C), 128.2, 128.0, 127.7, 126.7, 125.2, 122.4, 109.5, 68.3, 68.0, 61.0, 60.9, 60.2, 57.8, 51.7, 44.5, 44.0, 41.1, 33.8, 13.2; IR (Neat):3064, 3033, 2953, 1732, 1603, 1497, 1455, 1375, 1351, 1267, 1061, 1019; HRMS (ESI): calcd for $[M+H]^+$ $(C_{41}H_{39}O_9NCl)^+$ requires 724.2308; found 724.2302; enantiomeric excess: 99%, determined by HPLC (Chiralpak AD-H, hexane/*i*-PrOH 90/10, flow rate 0.7 mL/min; t_{major} = 117.3 min, t_{minor} = 102.9 min, λ = 254 nm).

*3,3-Dibenzyl-2-ethyl-(1R,2S,5R)-1′-benzyl-7′-chloro-5-(2-methoxy-2-oxoethyl)-2′-oxospiro[cyclopentane-1,3′-indoline]-2,3,3-tricarboxylate (**4da**).* 70 mg, yield 97%; colorless oil; $[\alpha]_D^{26.7}$ = +2.51 (*c* = 3.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.42 (dd, *J* = 7.6, 0.8 Hz, 1H), 7.20−7.33 (m, 15H), 7.14 (dd, *J* = 8.4, 0.8 Hz, 1H), 6.86 (t, *J* = 7.6 Hz, 1H), 5.41 (d, *J* = 15.6 Hz, 1H), 5.14−5.30 (m, 4H), 5.03 (d, *J* = 12.0 Hz, 1H), 4.91 (s, 1H), 3.65−3.71 (m, 1H), 3.50 (s, 3H), 3.48−3.52 (m, 1H), 2.81−2.94 (m, 3H), 1.77−1.89 (m, 2H), 0.50 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 178.3, 171.1, 170.8, 169.8, 168.3, 139.3, 137.6, 135.2, 131.4, 130.0, 128.5 (2C), 128.4, 128.3, 128.2, 127.3, 127.2, 124.1, 123.5, 115.5, 68.3, 68.0, 61.1, 60.9, 60.1, 57.9, 51.7, 45.6, 44.5, 41.1, 33.8, 13.3; IR (Neat): 3064, 3033,

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2952, 1732, 1607, 1489, 1455, 1440, 1377, 1266, 1185; HRMS (ESI): calcd for $[M+H]^+$ $(C_{41}H_{39}O_9NCl)^+$ requires 724.2308; found 724.2287; enantiomeric excess: 88%, determined by HPLC (Chiralpak AD-H, hexane/*i*-PrOH 75/25, flow rate 1.0 mL/min; t_{major} = 20.0 min, t_{minor} = 26.7 min, λ = 220 nm).

*3,3-Dibenzyl-2-ethyl-(1R,2S,5R)-1′-benzyl-5′-fluoro-5-(2-methoxy-2-oxoethyl)-2′-oxospiro[cyclopentane-1,3′-indoline]-2,3,3-tricarboxylate (**4ea**).* 64 mg, yield 90%; white solid; mp =116−117 °C; $[\alpha]_D^{27.1}$ = +7.88 (*c* = 3.10, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.39 (dd, *J* = 8.4, 2.4 Hz, 1H), 7.29−7.33 (m, 3H), 7.19−7.28 (m, 12H), 6.85 (td, *J* = 8.8, 2.4 Hz, 1H), 6.64 (dd, *J* = 8.8, 4.4 Hz, 1H), 5.21−5.26 (m, 2H), 5.15 (d, *J* = 12.4 Hz, 1H), 5.04−5.08 (m, 2H), 4.84 (s, 1H), 4.69 (d, *J* = 15.6 Hz, 1H), 3.61−3.69 (m, 1H), 3.49 (s, 3H), 3.41−3.47 (m, 1H), 2.94−2.98 (m, 1H), 2.72−2.85 (m, 2H), 1.79−1.90 (m, 2H), 0.41 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 177.1, 171.1, 170.8, 170.0, 168.2, 158.9 (d, J_{C-F} = 240.0 Hz), 139.2, 135.6, 135.2, 128.8, 128.5 (2C), 128.3, 128.2 (2C), 127.9, 127.7, 122.6, 115.1, 114.8, 114.2, 113.9, 109.4, 109.3, 68.3, 68.0, 61.1, 61.0, 60.8, 57.8, 51.7, 44.6, 44.1, 41.1, 33.8, 13.2; ^{19}F NMR ($CDCl_3$, 376 MHz) δ −119.2; IR (Neat):3064, 3033, 2953, 1739, 1606, 1491, 1454, 1369, 1269, 1180; HRMS (ESI): calcd for $[M+H]^+$ $(C_{41}H_{39}O_9NF)^+$ requires 708.2603; found 708.2593; enantiomeric excess: 90(98 after recrystallization)%, determined by HPLC (Chiralpak AD-H, hexane/*i*-PrOH 75/25, flow rate 1.0 mL/min; t_{major} = 34.0 min, t_{minor} = 41.2 min, λ = 254 nm).

*3,3-Dibenzyl-2-ethyl-(1R,2S,5R)-1′-benzyl-6′-fluoro-5-(2-methoxy-2-oxoethyl)-2′-oxospiro[cyclopentane-1,3′-indoline]-2,3,3-tricarboxylate (**4fa**).* 69 mg, yield 98%; colorless oil; $[\alpha]_D^{26.3}$ = +2.25 (*c* = 3.50, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.45 (t, *J* = 8.0 Hz, 2H), 7.22−7.37 (m, 14H), 6.60 (td, *J* = 8.8, 1.6 Hz, 1H), 6.48 (dd, *J* = 8.8, 1.6 Hz, 1H), 5.17−5.29 (m, 3H), 5.04−5.10 (m, 2H), 4.86 (s, 1H), 4.69 (d, *J* = 15.6 Hz, 1H), 3.59−3.65 (m, 1H), 3.52 (s, 3H), 3.44−3.49 (m, 1H), 2.82−2.96 (m, 3H), 1.82−1.90 (m, 2H), 0.43 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 177.7, 171.2, 170.8, 169.9, 168.4, 163.2 (d, J_{C-F} = 245 Hz), 144.9, 144.8, 135.4, 135.2, 128.8, 128.5 (2C), 128.3 (2C), 128.2, 128.0, 127.8, 127.0, 126.9, 122.1 (2C), 108.7, 108.5, 97.9, 97.7, 68.3, 68.0, 61.0, 60.8, 60.2, 57.8, 51.7, 44.6, 44.0, 41.1, 33.8, 13.2; ^{19}F NMR ($CDCl_3$, 376 MHz) δ −110.9; IR (Neat): 3064, 3033, 2952, 1732, 1613, 1498, 1456, 1382, 1344, 1266; HRMS (ESI): calcd for $[M+Na]^+$ $(C_{41}H_{38}O_9NFNa)^+$ requires 730.2423; found 730.2422; enantiomeric excess: 94%, determined by HPLC (Chiralpak PC-2, hexane/*i*-PrOH 90/10, flow rate 1.0 mL/min; t_{major} = 56.2 min, t_{minor} = 68.6 min, λ = 254 nm).

*3,3-Dibenzyl-2-ethyl-(1R,2S,5R)-1′-benzyl-7′-fluoro-5-(2-methoxy-2-oxoethyl)-2′-oxospiro[cyclopentane-1,3′-indoline]-2,3,3-tricarboxylate (**4ga**).* 68 mg, yield 96%; colorless oil; $[\alpha]_D^{27.1}$ = +1.77 (*c* = 2.40, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.40 (d, *J* = 7.6 Hz, 2H), 7.19−7.30 (m, 14H), 6.83−6.96 (m, 2H), 5.13−5.26 (m, 4H), 5.02 (d, *J* = 12.4 Hz, 1H), 4.87−4.91 (m, 2H), 3.54−3.62 (m, 1H), 3.49 (s, 3H), 3.30−3.39 (m, 1H), 2.80−2.92 (m, 3H), 1.72−1.85 (m, 2H), 0.33 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 177.2, 171.1, 170.9, 169.8, 168.3, 147.5 (d, J_{C-F} = 242.2 Hz), 137.1, 135.2, 129.9 (2C), 129.8, 128.5 (2C), 128.3, 128.2 (3C), 127.7, 123.3, 123.2, 121.5, 117.0, 116.8, 68.3, 68.0, 61.0, 60.9, 60.8 (2C), 60.7, 57.8, 51.7, 46.0, 45.9, 44.3, 41.0, 33.7, 13.1; ^{19}F NMR ($CDCl_3$, 376 MHz) δ −133.3; IR (Neat): 3064, 3033, 2953, 1731, 1629, 1487, 1476, 1455, 1351, 1265, 1189, 1069; HRMS (ESI): calcd for $[M+H]^+$ $(C_{41}H_{39}O_9NF)^+$ requires 708.2603; found 708.2594; enantiomeric excess: 90%, determined by HPLC (Chiralpak AD-H, hexane/*i*-PrOH 90/10, flow rate 0.8 mL/min; t_{major} = 77.7 min, t_{minor} = 72.7 min, λ = 220 nm).

*3,3-Dibenzyl-2-ethyl-(1R,2S,5R)-1′-benzyl-5-(2-methoxy-2-oxoethyl)-5′-methyl-2′-oxospiro[cyclopentane-1,3′-indoline]-2,3,3-tricarboxylate (**4ha**).* 65 mg, yield 92%; colorless oil; $[\alpha]_D^{26.2}$ = +12.04 (*c* = 3.15, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.20−7.34 (m, 16H), 6.92 (d, *J* = 8.0 Hz, 1H), 6.60 (d, *J* = 8.0 Hz, 1H), 5.21−5.27 (m, 2H), 5.15 (d, *J* = 12.4 Hz, 1H), 5.03−5.07 (m, 2H), 4.86 (s, 1H), 4.69 (d, *J* = 15.6 Hz, 1H), 3.52−3.58 (m, 1H), 3.48 (s, 3H), 3.37−3.45 (m, 1H), 2.78−2.92 (m, 3H), 2.21 (s, 3H), 1.83−1.85 (m, 2H), 0.35 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 177.3, 171.4, 170.9, 169.7, 168.6, 140.8, 136.1, 135.4, 135.3, 132.1, 129.0, 128.7, 128.6, 128.5 (2C), 128.3, 128.2, 128.1 (2C), 127.8, 127.7, 126.9, 126.4, 108.7, 68.2, 67.7, 61.2, 60.6, 60.5, 57.6, 51.6, 44.4, 43.8, 40.9, 34.0, 21.2, 13.1; IR (Neat): 3063, 3032, 2952, 1739, 1618, 1497, 1455, 1370, 1265, 1195; HRMS (ESI): calcd for $[M+H]^+$ $(C_{42}H_{42}O_9N)^+$ requires 704.2854; found 704.2831; enantiomeric excess: 91%, determined by HPLC (Chiralpak AD-H, hexane/*i*-PrOH 75/25, flow rate 0.7 mL/min; t_{major} = 43.3 min, t_{minor} = 78.9 min, λ = 254 nm).

*3,3-Dibenzyl-2-ethyl-(1R,2S,5R)-1′-benzyl-5-(2-methoxy-2-oxoethyl)-7′-methyl-2′-oxospiro[cyclopentane-1,3′-indoline]-2,3,3-tricarboxylate (**4ia**).* 56 mg, yield 80%; white solid; mp =39−40 °C; $[\alpha]_D^{24.7}$ = −2.25 (*c* = 2.70, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.24−7.35 (m, 16H), 6.93 (d, *J* = 7.2 Hz, 1H), 6.86 (t, *J* = 7.6 Hz, 1H), 5.35 (d, *J* = 16.8 Hz, 1H), 5.25−5.29 (m, 2H), 5.17 (d, 16.0 Hz, 1H), 5.02−5.08 (m, 2H), 4.93 (s, 1H), 3.71−3.77 (m, 1H), 3.56−3.69 (m, 1H), 3.52 (s, 3H), 2.82−2.98 (m, 3H), 2.28 (s, 3H), 1.84−1.97 (m, 2H), 0.56 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 177.2, 171.1, 170.8, 169.9, 168.3, 144.6, 135.4, 135.2, 128.9, 128.5 (2C), 128.3 (2C), 128.2, 128.0, 127.7, 127.0, 125.8, 125.4, 122.5, 112.3, 68.3, 68.0, 61.0, 60.9, 60.3, 57.8, 51.7, 44.5, 44.0, 41.1, 33.8, 27.0, 13.2; IR (Neat): 3032, 2953, 1732, 1600, 1497, 1453, 1374, 1357, 1265, 1188; HRMS (ESI): calcd for $[M+Na]^+$ $(C_{42}H_{41}O_9NNa)^+$ requires 726.2674; found 726.2653; enantiomeric excess: 91%, determined by HPLC (Chiralpak AD-H, hexane/*i*-PrOH 75/25, flow rate 1.0 mL/min; t_{major} = 26.1 min, t_{minor} = 69.0 min, λ = 220 nm).

*3,3-Dibenzyl-2-ethyl-(1R,2S,5R)-1′-benzyl-5′-methoxy-5-(2-methoxy-2-oxoethyl)-2′-oxospiro[cyclopentane-1,3′-indoline]-2,3,3-tricarboxylate (**4ja**).* 70 mg, yield 97%; colorless oil; $[\alpha]_D^{26.5}$ = +11.60 (*c* = 2.90, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.22−7.37 (m, 16H), 6.69 (dd, *J* = 8.4, 2.4 Hz, 1H), 6.64 (d, *J* = 8.4 Hz, 1H), 5.27 (d, *J* = 12.4 Hz, 1H), 5.16 (d, *J* = 12.4 Hz, 1H), 5.03−5.09 (m, 2H), 4.88 (s, 1H), 4.74 (d, *J* = 15.2 Hz, 1H), 3.74 (s, 3H), 3.62−3.67 (m, 1H), 3.52 (s, 3H), 3.45−3.52 (m, 1H), 2.84−2.98 (m, 3H), 1.86−1.94 (m, 2H), 0.42 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 177.0, 171.4, 171.0, 170.0, 168.4, 155.9, 136.6, 136.1, 135.4, 135.3, 128.7, 128.5, 128.4, 128.3, 128.2, 128.1 (2C), 128.0, 127.8, 127.7, 113.4, 112.9, 109.3, 68.2, 67.8, 61.1, 61.0, 60.7, 57.6, 55.8, 51.6, 44.5, 44.0, 41.0, 33.9, 13.2; IR (Neat): 3064, 3032, 2952, 1732, 1599, 1499, 1494, 1455, 1436, 1307, 1267; HRMS (ESI): calcd for $[M+Na]^+$ $(C_{42}H_{41}O_{10}NNa)^+$ requires 742.2623; found 742.2634; enantiomeric excess: 94%, determined by HPLC (Chiralpak AD-H, hexane/*i*-PrOH 80/20, flow rate 1.0 mL/min; t_{major} = 48.6 min, t_{minor} = 70.2 min, λ = 254 nm).

*3,3-Dibenzyl-2-ethyl-(1R,2S,5R)-1′-benzyl-6′-methoxy-5-(2-methoxy-2-oxoethyl)-2′-oxospiro[cyclopentane-1,3′-indoline]-2,3,3-tricarboxylate (**4ka**).* 65 mg, yield 90%; colorless oil; $[\alpha]_D^{26.3}$ = −0.93 (*c* = 2.60, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.22−7.40 (m, 16H), 6.41 (d, *J* = 8.0 Hz, 1H), 6.34 (s, 1H), 5.24−5.28 (m, 2H), 5.17 (d, *J* = 12.4 Hz, 1H), 5.02−5.06 (m, 2H), 4.85 (s, 1H), 4.71 (d, *J* = 15.6 Hz, 1H), 3.71 (s, 3H), 3.56−3.62 (m, 1H), 3.51 (s, 3H), 3.45−3.49 (m, 1H), 2.78−2.93 (m, 3H), 1.85−1.87 (m, 2H), 0.44 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 177.9, 171.4, 170.9, 169.9, 168.6, 160.4, 144.5, 135.9, 135.4, 135.3, 128.7, 128.5 (2C), 128.2 (2C), 127.8, 126.5, 118.5, 105.8, 97.4, 68.2, 67.8, 61.0, 60.7, 60.2, 57.7, 55.4, 51.6, 44.5, 43.9, 41.0, 33.9, 13.2; IR (Neat): 3064, 3032, 2953, 1731, 1624, 1595, 1502, 1456, 1438, 1382, 1269; HRMS (ESI): calcd for $[M+Na]^+$ $(C_{42}H_{41}O_{10}NNa)^+$ requires 742.2623; found 742.2644; enantiomeric excess: 92%, determined by HPLC (Chiralpak AD-H, hexane/*i*-PrOH 75/25, flow rate 1.0 mL/min; t_{major} = 32.4 min, t_{minor} = 73.4 min, λ = 254 nm).

*3,3-Dibenzyl-2-ethyl-(1R,2S,5R)-1′-benzyl-5-(2-methoxy-2-oxoethyl)-2′-oxo-5′-(trifluoromethoxy)spiro[cyclopentane-1,3′-indoline]-2,3,3-tricarboxylate (**4la**).* 74 mg, yield 96%; colorless oil; $[\alpha]_D^{27.1}$ = +1.94 (*c* = 3.8, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.52 (d, *J* = 1.2 Hz, 1H), 7.19−7.34 (m, 15H), 7.03 (dd, *J* = 8.4, 1.2 Hz, 1H), 6.69 (d, *J* = 8.4 Hz, 1H), 5.05−5.26 (m, 5H), 4.82 (s, 1H), 4.68 (d, *J* = 15.6 Hz, 1H), 3.60−3.69 (m, 1H), 3.50 (s, 3H), 3.38−3.49 (m, 1H), 2.96−3.00 (m, 1H), 2.71−2.88 (m, 2H), 1.85−1.87 (m, 2H), 0.38 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 177.3, 171.1, 170.7, 169.8, 168.1, 144.5, 142.0, 135.4, 135.3, 135.2, 128.8, 128.5 (2C), 128.3, 128.2, 128.1, 128.0, 127.7, 121.7, 109.2, 68.3, 68.0, 61.1, 60.8, 60.6, 57.9, 51.7, 44.6, 44.1, 41.2, 33.9, 13.1; ^{19}F NMR ($CDCl_3$,

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376 MHz) δ −58.4; IR (Neat): 3066, 3034, 2953, 1733, 1619, 1491, 1455, 1371, 1346, 1259; HRMS (ESI): calcd for $[M+Na]^+$ $(C_{42}H_{38}O_{10}NF_3Na)^+$ requires 796.2340; found 796.2378; enantiomeric excess: 94%, determined by HPLC (Chiralpak AD-H, hexane/*i*-PrOH 85/15, flow rate 1.0 mL/min; t_{major} = 24.7 min, t_{minor} = 31.5 min, λ = 220 nm).

3,3-Dibenzyl-2-ethyl-(1R,2S,5R)-1′-benzyl-5′-iodo-5-(2-methoxy-2-oxoethyl)-2′-oxospiro[cyclopentane-1,3′-indoline]-2,3,3-tricarboxylate (**4ma**). 77 mg, yield 94%; white solid; mp =42−43 °C; $[\alpha]_D^{28.3}$ = +13.62 (*c* = 3.50, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.81 (d, *J* = 1.2 Hz, 1H), 7.47 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.20−7.32 (m, 15H), 6.49 (d, *J* = 7.6 Hz, 1H), 5.21−5.26 (m, 2H), 5.15 (d, *J* = 12.4 Hz, 1H), 5.04−5.10 (m, 2H), 4.78 (s, 1H), 4.68 (d, *J* = 15.6 Hz, 1H), 3.59−3.67 (m, 1H), 3.49 (s, 3H), 3.39−3.47 (m, 1H), 2.94−2.98 (m, 1H), 2.72−2.88 (m, 2H), 1.88−1.90 (m, 2H), 0.43 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 176.7, 171.1, 170.8, 169.7, 168.2, 143.0, 137.6, 135.4, 135.3, 135.2, 134.2, 129.5, 128.8, 128.5 (2C), 128.3, 128.2, 127.9, 127.6, 111.0, 85.1, 68.3, 67.9, 61.2, 60.9, 60.2, 58.0, 51.7, 44.4, 44.0, 41.1, 33.9, 13.2; IR (Neat): 3033, 2918, 2849, 1737, 1603, 1497, 1484, 1345, 1266, 1178; HRMS (ESI): calcd for $[M+Na]^+$ $(C_{41}H_{38}O_9NINa)^+$ requires 838.1483; found 838.1477; enantiomeric excess: 86%, determined by HPLC (Chiralpak AD-H, hexane/*i*-PrOH 75/25, flow rate 1.0 mL/min; t_{major} = 55.0 min, t_{minor} = 69.6 min, λ = 220 nm).

3,3-Dibenzyl-2-ethyl-(1R,2S,5R)-1′-benzyl-5′-bromo-5-(2-methoxy-2-oxoethyl)-2′-oxospiro[cyclopentane-1,3′-indoline]-2,3,3-tricarboxylate (**4na**). 63 mg, yield 82%; colorless oil; $[\alpha]_D^{27.1}$ = +15.79 (*c* = 2.80, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.67 (d, *J* = 2.0 Hz, 1H), 7.20−7.32 (m, 16H), 6.59 (d, *J* = 8.4 Hz, 1H), 5.21−5.26 (m, 2H), 5.15 (d, *J* = 12.0 Hz, 1H), 5.05−5.09 (m, 2H), 4.79 (s, 1H), 4.68 (d, *J* = 15.6 Hz, 1H), 3.60−3.67 (m, 1H), 3.50 (s, 3H), 3.40−3.49 (m, 1H), 2.94−2.99 (m, 1H), 2.72−2.94 (m, 2H), 1.88 (d, *J* = 7.2 Hz, 2H), 0.43 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 176.9, 171.1, 170.8, 169.8, 168.2, 142.4, 135.4, 135.3, 135.2, 131.6, 129.1, 128.8, 128.7, 128.5 (2C), 128.3, 128.2, 127.9, 127.7, 115.3, 110.4, 68.3, 67.9, 61.2, 60.8, 60.5, 58.0, 51.7, 44.5, 44.1, 41.1, 33.9, 13.2; IR (Neat): 3065, 3033, 1952, 1739, 1607, 1482, 1497, 1455, 1344, 1267, 1178; HRMS (ESI): calcd for $[M+Na]^+$ $(C_{41}H_{38}O_9NBrNa)^+$ requires 790.1622; found 790.1614; enantiomeric excess: 87%, determined by HPLC (Chiralpak AD-H, hexane/*i*-PrOH 80/20, flow rate 1.0 mL/min; t_{major} = 60.1 min, t_{minor} = 72.8 min, λ = 220 nm).

3,3-Dibenzyl-2-ethyl-(1R,2S,5R)-1′-benzyl-7′-bromo-5-(2-methoxy-2-oxoethyl)-2′-oxospiro[cyclopentane-1,3′-indoline]-2,3,3-tricarboxylate (**4oa**). 74 mg, yield 97%; colorless oil; $[\alpha]_D^{27.1}$ = +2.28 (*c* = 2.90, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.53 (dd, *J* = 7.6, 0.8 Hz, 1H), 7.25−7.41 (m, 16H), 6.87 (t, *J* = 8.0 Hz, 1H), 5.40−5.53 (m, 2H), 5.29−5.32 (m, 2H), 5.21 (d, *J* = 12.4 Hz, 1H), 5.11 (d, *J* = 12.4 Hz, 1H), 4.97 (s, 1H), 3.75−3.80 (m, 1H), 3.56−3.62 (m, 1H), 3.50 (s, 3H), 2.88−3.00 (m, 3H), 1.89−1.93 (m, 2H), 0.61 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 178.3, 171.1, 170.8, 169.8, 168.3, 139.3, 137.6, 135.2, 131.4, 130.0, 128.5 (2C), 128.4, 128.3, 128.2, 127.3, 127.2, 124.1, 123.5, 115.5, 68.3, 68.0, 61.1, 60.9, 60.1, 57.9, 51.7, 45.6, 44.5, 41.1, 33.8, 13.3; IR (Neat): 3032, 1952, 1739, 1603, 1497, 1453, 1350, 1265, 1195; HRMS (ESI): calcd for $[M+H]^+$ $(C_{41}H_{39}O_9NBr)^+$ requires 768.1803; found 768.1798; enantiomeric excess: 82%, determined by HPLC (Chiralpak AD-H, hexane/*i*-PrOH 80/20, flow rate 1.0 mL/min; t_{major} = 27.9 min, t_{minor} = 48.2 min, λ = 254 nm).

2-Ethyl-3,3-dimethyl-(1R,2S,5R)-1′-benzyl-5-(2-methoxy-2-oxoethyl)-2′-oxospiro[cyclopentane-1,3′-indoline]-2,3,3-tricarboxylate (**4ab**). 53 mg, yield 99%; colorless oil; $[\alpha]_D^{26.5}$ = −0.61 (*c* = 3.05, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.56 (d, *J* = 7.6 Hz, 1H), 7.38−7.40 (m, 2H), 7.24−7.33 (m, 3H), 7.18 (t, *J* = 7.6 Hz, 1H), 7.00 (t, *J* = 7.6 Hz, 1H), 6.77 (d, *J* = 7.6 Hz, 1H), 5.09 (d, *J* = 15.2 Hz, 1H), 4.83 (s, 1H), 4.75 (d, *J* = 15.6 Hz, 1H), 3.87 (s, 3H), 3.78 (s, 3H), 3.59−3.65 (m, 1H), 3.54 (s, 3H), 3.44−3.49 (m, 1H), 2.81−2.96 (m, 3H), 1.86−1.88 (m, 2H), 0.37 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 177.4, 171.7, 171.4, 170.7, 168.5, 143.2, 135.9, 128.7 (2C), 127.8 (2C), 126.8, 125.6, 122.7, 109.0, 60.8, 60.7, 60.6, 53.6, 53.1, 51.6, 44.4, 44.0, 41.1, 33.9, 13.0; IR (Neat): 3064, 2953, 1738, 1611, 1489, 1467, 1436, 1369, 1274, 1191, 1366, 1177; HRMS (ESI): calcd for $[M+H]^+$ $(C_{29}H_{32}O_9N)^+$ requires 538.2072; found 538.2066; enantiomeric excess: 82%, determined by HPLC (Chiralpak PC-2, hexane/*i*-PrOH 80/20, flow rate 0.7 mL/min; t_{major} = 65.8 min, t_{minor} = 58.3 min, λ = 254 nm).

Triethyl-(1R,2S,5R)-1′-benzyl-5-(2-methoxy-2-oxoethyl)-2′-oxospiro[cyclopentane-1,3′-indoline]-2,3,3-tricarboxylate (**4ac**). 56 mg, yield 99%; colorless oil; $[\alpha]_D^{27.1}$ = +2.73 (*c* = 2.70, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.55 (d, *J* = 7.6 Hz, 1H), 7.37−7.39 (m, 2H), 7.24−7.33 (m, 3H), 7.17 (td, *J* = 7.6, 0.8 Hz, 1H), 6.99 (td, *J* = 7.6, 0.8 Hz, 1H), 6.76 (d, *J* = 8.0 Hz, 1H), 5.09 (d, *J* = 15.2 Hz, 1H), 4.84 (s, 1H), 4.76 (d, *J* = 15.2 Hz, 1H), 4.28−4.39 (m, 3H), 4.14−4.22 (m, 1H), 3.59−3.67 (m, 1H), 3.54 (s, 3H), 3.43−3.51 (m, 1H), 2.82−2.93 (m, 3H), 1.84−1.89 (m, 2H), 1.33 (t, *J* = 7.2 Hz, 3H), 1.26 (t, *J* = 7.2 Hz, 3H), 0.39 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 177.4, 171.4, 171.1, 170.2, 168.5, 143.2, 136.0, 128.7, 127.8, 126.9, 125.7, 122.5, 108.9, 62.5, 62.0, 60.9, 60.5, 57.5, 51.6, 44.4, 43.9, 41.0, 33.9, 14.0, 13.8, 13.1; IR (Neat): 2981, 1731, 1611, 1489, 1467, 1438, 1367, 1267, 1186; HRMS (ESI): calcd for $[M+H]^+$ $(C_{31}H_{36}O_9N)^+$ requires 566.2385; found 566.2379; enantiomeric excess: 89%, determined by HPLC (Chiralpak AD-H, hexane/*i*-PrOH 90/10, flow rate 0.7 mL/min; t_{major} = 39.4 min, t_{minor} = 64.4 min, λ = 254 nm).

2-Ethyl-3,3-dimethyl-(1R,2S,5R)-1′-benzyl-2′-oxo-5-(2-oxopropyl)spiro[cyclopentane-1,3′-indoline]-2,3,3-tricarboxylate (**4ad**). 47 mg, yield 90%; colorless oil; $[\alpha]_D^{24.9}$ = −8.19 (*c* = 1.40, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.50 (d, *J* = 7.6 Hz, 1H), 7.29−7.36 (m, 5H), 7.15 (td, *J* = 7.6, 0.8 Hz, 1H), 7.01 (t, *J* = 7.6 Hz, 1H), 6.70 (d, *J* = 7.6 Hz, 1H), 5.10 (d, *J* = 15.6 Hz, 1H), 4.75 (d, *J* = 15.6 Hz, 1H), 4.23 (s, 1H), 3.87 (s, 3H), 3.79 (s, 3H), 3.60−3.65 (m, 3H), 2.82 (dd, *J* = 13.2, 6.4 Hz, 1H), 2.48 (dd, *J* = 16.8, 6.0 Hz, 1H), 2.26 (t, *J* = 12.8 Hz, 1H), 2.15 (dd, *J* = 16.8, 4.4 Hz, 1H), 1.92 (s, 3H), 0.49 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 205.9, 178.9, 171.6, 171.3, 169.1, 142.8, 135.8, 130.1, 128.7, 128.5, 127.8, 127.5, 125.2, 123.3, 108.6, 61.4, 60.7, 58.8, 58.7, 53.4, 53.0, 44.6, 43.9, 43.8, 39.6, 29.8, 13.2; IR (Neat): 2953, 2924, 1732, 1611, 1489, 1467, 1435, 1370, 1279, 1243, 1180; HRMS (ESI): calcd for $[M+H]^+$ $(C_{29}H_{32}O_8N)^+$ requires 522.2122; found 522.2118; enantiomeric excess: 87%, determined by HPLC (Chiralpak IC, hexane/*i*-PrOH 70/30, flow rate 1.0 mL/min; t_{major} = 47.0 min, t_{minor} = 25.3 min, λ = 220 nm).

2-Ethyl-3,3-dimethyl-(1R,2S,5R)-1′-benzyl-2′-oxo-5-(2-oxo-2-phenylethyl)spiro[cyclopentane-1,3′-indoline]-2,3,3-tricarboxylate (**4ae**). 57 mg, yield 97%; white solid; mp =38−39 °C; $[\alpha]_D^{26.9}$ = −5.53 (*c* = 3.3, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.63 (d, *J* = 7.2 Hz, 1H), 7.55−7.57 (m, 2H), 7.50 (t, *J* = 7.2 Hz, 1H), 7.32−7.39 (m, 4H), 7.15−7.28 (m, 4H), 7.03 (t, *J* = 7.2 Hz, 1H), 6.73 (d, *J* = 7.6 Hz, 1H), 5.01 (d, *J* = 15.6 Hz, 1H), 4.90 (s, 1H), 4.75 (d, *J* = 15.2 Hz, 1H), 3.89 (s, 3H), 3.80 (s, 3H), 3.60−3.68 (m, 1H), 3.46−3.54 (m, 1H), 2.86−3.10 (m, 3H), 2.63 (dd, *J* = 16.8, 4.8 Hz, 1H), 2.42 (dd, *J* = 16.8, 8.0 Hz, 1H), 0.41 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 197.3, 177.6, 171.7, 170.8, 168.7, 143.2, 136.5, 136.1, 133.1, 128.7, 128.5, 127.8 (2C), 127.7, 125.6, 122.6, 109.0, 60.9, 60.7, 60.6, 60.9, 57.6, 53.6, 53.1, 44.4, 43.7, 41.2, 37.9, 13.1; IR (Neat): 3060, 2980, 2953, 1732, 1687, 1610, 1489, 1467, 1449, 1368, 1273, 1201; HRMS (ESI): calcd for $[M+H]^+$ $(C_{34}H_{34}O_8N)^+$ requires 584.2279; found 584.2271; enantiomeric excess: 89%, determined by HPLC (Chiralpak AD-H, hexane/*i*-PrOH 75/25, flow rate 1.0 mL/min; t_{major} = 14.3 min, t_{minor} = 43.6 min, λ = 220 nm).

3,3-Dibenzyl-2-methyl-(1R,2S,5R)-1′-benzyl-5-(2-methoxy-2-oxoethyl)-2′-oxospiro[cyclopentane-1,3′-indoline]-2,3,3-tricarboxylate (**4pa**). 67 mg, yield 99%; colorless oil; $[\alpha]_D^{28.7}$ = +3.41 (*c* = 0.95, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.44 (d, *J* = 7.2 Hz, 1H), 7.32−7.34 (m, 2H), 7.18−7.29 (m, 13H), 7.13 (t, *J* = 7.6 Hz, 1H), 6.91 (t, *J* = 7.6 Hz, 1H), 6.72 (d, *J* = 8.0 Hz, 1H), 5.15−5.26 (m, 4H), 5.04 (d, *J* = 12.0 Hz, 1H), 4.89 (s, 1H), 4.62 (d, *J* = 15.6 Hz, 1H), 3.47 (s, 3H), 2.91−2.94 (m, 1H), 2.88 (s, 3H), 2.83−2.86 (m, 1H), 1.84−1.91 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 177.2, 171.3 170.9, 169.7, 169.0, 143.0, 135.9, 135.3, 128.7, 128.5 (2C), 128.3, 128.2, 127.7 (2C), 126.6, 125.6, 122.6, 109.0, 68.3, 67.9, 61.0, 60.6, 57.8, 51.6, 51.4, 44.3, 43.7, 41.1, 33.9; IR (Neat): 3063, 3032, 2951, 1739, 1611, 1489, 1466, 1455, 1436, 1367, 1266, 1178; HRMS (ESI): calcd for [M

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+H]$^+$ ($C_{40}H_{38}O_9N$)$^+$ requires 676.2541; found 676.2540; enantiomeric excess: 92%, determined by HPLC (Chiralpak AD-H, hexane/*i*-PrOH 75/25, flow rate 1.0 mL/min; t_{major} = 46.0 min, t_{minor} = 55.8 min, λ = 254 nm).

*3,3-Dibenzyl-1′-(tert-butyl)-2-ethyl-(1R,2S,5R)-5-(2-methoxy-2-oxoethyl)-2′-oxospiro[cyclopentane-1,3′-indoline]-1′,2,3,3-tetracarboxylate (**4qa**).* 68 mg, yield 97%; colorless oil; $[\alpha]_D^{26.9}$ = −13.73 (*c* = 3.4, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.81 (d, *J* = 8.4 Hz, 1H), 7.49 (d, *J* = 7.2 Hz, 1H), 7.14−7.26 (m, 11H), 7.02 (td, *J* = 7.6, 0.8 Hz, 1H), 5.16−5.23 (m, 2H), 5.07−5.10 (m, 1H), 4.98 (d, *J* = 12.0 Hz, 1H), 4.83 (s, 1H), 3.42−3.50 (m, 2H), 3.42 (s, 3H), 2.77−2.85 (m, 3H), 1.85−1.87 (m, 2H), 1.58 (s, 9H), 0.57 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 176.1, 171.1, 170.9, 169.7, 168.2, 168.1, 149.1, 140.2, 135.3, 135.2, 129.0, 128.9, 128.6, 128.5 (2C), 128.3, 128.2, 128.0, 125.7, 125.2, 124.4, 121.9, 114.9, 84.5, 68.3, 68.0, 61.2, 60.9, 60.5, 58.9, 51.6, 44.5, 41.2, 34.0, 28.1, 13.1; IR (Neat): 3033, 2981, 2953, 1731, 1606, 1498, 1482, 1465, 1370, 1256, 1152; HRMS (ESI): calcd for [M+H]$^+$ ($C_{39}H_{42}O_{11}N$)$^+$ requires 700.2752; found 700.2749; enantiomeric excess: 87%, determined by HPLC (Chiralpak AD-H, hexane/*i*-PrOH 90/10, flow rate 0.7 mL/min; t_{major} = 16.4 min, t_{minor} = 18.0 min, λ = 254 nm).

*3,3-Dibenzyl-2-ethyl-(1R,2S,5R)-5-(2-methoxy-2-oxoethyl)-1′-methyl-2′-oxospiro[cyclopentane-1,3′-indoline]-2,3,3-tricarboxylate (**4ra**).* 60 mg, yield 98%; colorless oil; $[\alpha]_D^{26.6}$ = −10.55 (*c* = 3.40, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.53 (d, *J* = 7.6 Hz, 1H), 7.22−7.30 (m, 11H), 6.98 (t, *J* = 7.6 Hz, 1H), 6.82 (d, *J* = 7.6 Hz, 1H), 5.24−5.29 (m, 2H), 5.17 (d, *J* = 12.0 Hz, 1H), 5.06 (d, *J* = 12.4 Hz, 1H), 4.81 (s, 1H), 3.52−3.60 (m, 2H), 3.49 (s, 3H), 3.23 (s, 3H), 2.78−2.97 (m, 3H), 1.87 (d, *J* = 6.8 Hz, 2H), 0.60 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 177.2, 171.3, 171.0, 169.9, 168.4, 144.1, 135.3 (2C), 128.9, 128.5 (2C), 128.3, 128.2 (3C), 126.7, 125.7, 122.6, 107.9, 68.2, 67.9, 60.9, 60.7, 60.5, 57.7, 51.6, 43.6, 41.1, 33.9, 26.7, 13.3; IR (Neat): 3062, 3033, 2952, 1731, 1611, 1495, 1470, 1421, 1377, 1351, 1266, 1094; HRMS (ESI): calcd for [M+Na]$^+$ ($C_{35}H_{35}O_9NNa$)$^+$ requires 636.2204; found 636.2213; enantiomeric excess: 85%, determined by HPLC (Chiralpak AD-H, hexane/*i*-PrOH 75/25, flow rate 1.0 mL/min; t_{major} = 22.5 min, t_{minor} = 20.6 min, λ = 254 nm).

*3,3-Dibenzyl-1′-(tert-butyl)-(1R,2S,5R)-2-benzoyl-5-(2-methoxy-2-oxoethyl)-2′-oxospiro[cyclopentane-1,3′-indoline]-1′,3,3-tricarboxylate (**4sa**).* 62 mg, yield 85%; colorless oil; $[\alpha]_D^{28.1}$ = −58.13 (*c* = 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.43 (d, *J* = 7.6 Hz, 1H), 7.30−7.35 (m, 3H), 7.24−7.28 (m, 6H), 7.01−7.20 (m, 9H), 5.88 (s, 1H), 5.22−5.27 (m, 2H), 4.15 (d, *J* = 12.4 Hz, 1H), 4.97 (d, *J* = 12.4 Hz, 1H), 3.44 (s, 3H), 2.84−3.04 (m, 3H), 1.89−1.92 (m, 2H), 1.54 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 196.7, 176.1, 171.7, 170.9, 169.4, 148.4, 139.4, 136.8, 135.3, 135.2, 132.9, 129.0, 128.6, 128.4, 128.2, 128.1, 126.5, 124.4 (2C), 114.5, 84.3, 68.3, 67.7, 61.6, 61.3, 61.1, 51.6, 44.7, 40.7, 34.1, 28.1; IR (Neat): 2955, 2923, 2852, 1735, 1679, 1483, 1458, 1388, 1262, 1160, 1095; HRMS (ESI): calcd for [M+H]$^+$ ($C_{43}H_{42}O_{10}N$)$^+$ requires 732.2803; found 732.2797; enantiomeric excess: 91%, determined by HPLC (Chiralpak PC-2, hexane/*i*-PrOH 90/10, flow rate 1.0 mL/min; t_{major} = 28.7 min, t_{minor} = 19.9 min, λ = 254 nm).

*Dibenzyl-(1R,2S,5R)-2-benzoyl-5-(2-methoxy-2-oxoethyl)-2′-oxospiro[cyclopentane-1,3′-indoline]-3,3-dicarboxylate (**5**).* 59 mg, yield 94%; white solid; mp =58−60 °C; $[\alpha]_D^{28.7}$ = −30.59 (*c* = 1.0, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.27 (br, 1H), 7.36 (d, *J* = 7.2 Hz, 2H), 7.14−7.26 (m, 7H), 7.05−7.12 (m, 5H), 6.97−7.01 (m, 3H), 6.91 (t, *J* = 7.2 Hz, 1H), 6.47 (d, *J* = 7.6 Hz, 1H), 5.78 (s, 1H), 5.09−5.14 (m, 3H), 4.88 (d, *J* = 12.4 Hz, 1H), 3.34 (s, 3H), 2.85−2.95 (m, 2H), 2.77 (dd, *J* = 11.6, 4.0 Hz, 1H), 1.87 (d, *J* = 6.4 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 196.7, 179.5, 171.6, 171.2, 169.3, 140.3, 136.6, 135.2, 135.1, 133.0, 128.7, 128.5, 128.3 (2C), 128.2 (2C), 128.1 (2C), 128.0, 127.3, 125.8, 122.7, 109.7, 68.3, 67.6, 61.6, 61.3, 61.1, 59.4, 51.6, 43.7, 40.5, 33.8; IR (Neat): 3310, 3063, 2952, 1732, 1619, 1497, 1472, 1486, 1448, 1264, 1203; HRMS (ESI): calcd for [M+H]$^+$ ($C_{38}H_{34}O_8N$)$^+$ requires 632.2279; found 632.2276; enantiomeric excess: 91%, determined by HPLC (Chiralpak PC-2, hexane/*i*-PrOH 75/25, flow rate 1.0 mL/min; t_{major} = 22.4 min, t_{minor} = 12.9 min, λ = 254 nm).

*3,3-Dibenzyl-2-ethyl-(1R,2S,5R)-1′-acetyl-5-(2-methoxy-2-oxoethyl)-2′-oxospiro[cyclopentane-1,3′-indoline]-2,3,3-tricarboxylate (**4ta**).* 62 mg, yield 97%; colorless oil; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.14 (d, *J* = 8.0 Hz, 1H), 7.11−7.28 (m, 13H), 5.12−5.22 (m, 3H), 5.06 (d, *J* = 12.0 Hz, 1H), 4.10 (s, 1H), 3.62−3.71 (m, 1H), 3.46−3.53 (m, 1H), 3.35 (s, 3H), 2.94−3.00 (m, 1H), 2.65−2.71 (m, 1H), 2.59 (s, 3H), 2.10−2.23 (m, 1H), 1.94−1.99 (m, 1H), 0.77 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 177.7, 172.2, 171.3, 170.7, 169.0, 168.3, 141.0, 135.2, 135.1, 129.3, 128.8, 128.6, 128.5, 128.4, 128.3, 128.1, 127.5, 125.3, 121.7, 116.5, 68.2, 68.0, 61.1, 61.0, 60.8, 58.7, 51.8, 45.3, 39.4, 33.6, 26.7, 13.5; IR (Neat): 3033, 2953, 1739, 1489, 1479, 1464, 1372, 1267; HRMS (ESI): calcd for [M+H]$^+$ ($C_{36}H_{36}O_{10}N$)$^+$ requires 642.2334; found 642.2337; enantiomeric excess: 27%, determined by HPLC (Chiralpak ADH, hexane/*i*-PrOH 90/10, flow rate 1.0 mL/min; t_{major} = 25.2 min, t_{minor} = 30.8 min, λ = 254 nm).

*Dibenzyl-(1R,2S,5R)-1′-benzyl-5-(2-methoxy-2-oxoethyl)-2′-oxo-2-phenylspiro[cyclopentane-1,3′-indoline]-3,3-dicarboxylate (**4ua**).* 42 mg, yield 60%; white solid; mp =142−144 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.99−8.01 (m, 1H), 6.98−7.18 (m, 12H), 6.88−6.93 (m, 4H), 6.83−6.85 (m, 2H), 6.55−6.56 (m, 2H), 6.34−6.36 (m, 3H), 5.14 (d, *J* = 16.0 Hz, 1H), 5.04 (d, *J* = 3.2 Hz, 2H), 5.01 (s, 1H), 4.80 (d, *J* = 12.4 Hz, 1H), 4.35 (d, *J* = 16.0 Hz, 1H), 4.34 (d, *J* = 12.4 Hz, 1H), 3.48 (s, 3H), 3.24−3.33 (m, 1H), 2.97−3.08 (m, 1H), 2.79 (dd, J = 7.2 7.2 Hz, 1H), 1.92−2.08 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 177.2, 171.8, 171.7, 170.5, 143.1, 135.2, 135.1, 134.9, 134.5, 130.4, 128.7, 128.5, 128.4, 128.2 (3C), 128.0, 127.9, 127.7, 127.6, 127.0, 126.5, 126.1, 122.3, 109.6, 68.0, 67.5, 63.9, 63.6, 60.3, 51.6, 43.6, 42.9, 40.3, 34.6; IR (Neat): 3063, 3033, 2951, 1731, 1610, 1493, 1467, 1455, 1367, 1262, 1181, 1095; HRMS (ESI): calcd for [M+H]$^+$ ($C_{44}H_{40}O_7N$)$^+$ requires 694.2799; found 694.2800; enantiomeric excess: 14%, determined by HPLC (Chiralpak ADH, hexane/*i*-PrOH 75/25, flow rate 1.0 mL/min; t_{major} = 47.0 min, t_{minor} = 96.8 min, λ = 254 nm).

*Dibenzyl-(1R,2S,5R)-2-benzoyl-1′-benzyl-5-(2-methoxy-2-oxoethyl)-2′-oxospiro[cyclopentane-1,3′-indoline]-3,3-dicarboxylate (**4va**).* 68 mg, yield 95%; colorless oil; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.52 (d, *J* = 7.2 Hz, 2H), 7.43−7.47 (m, 2H), 7.29−7.34 (m, 5H), 7.13−7.26 (m, 10H), 7.02−7.10 (m, 2H), 6.93 (d, *J* = 7.2 Hz, 2H), 6.42 (d, *J* = 8.4 Hz, 1H), 6.00 (s, 1H), 5.25−5.25 (m, 2H), 5.22 (d, *J* = 12.0 Hz, 1H), 5.02 (d, *J* = 12.4 Hz, 1H), 4.66 (d, *J* = 15.6 Hz, 1H), 4.52 (d, *J* = 15.6 Hz, 1H), 3.52 (s, 3H), 3.01−3.16 (m, 3H), 1.89−1.96 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 196.6, 177.1, 171.4, 171.0, 169.5, 142.4, 136.8, 135.4, 135.3, 135.2, 133.1, 128.7 (2C), 128.5 (2C), 128.3 (2C), 128.2, 128.0, 127.5, 127.3, 127.1, 125.4, 122.7, 109.0, 68.3, 67.7, 61.8, 61.2, 59.2, 51.6, 44.3, 44.2, 40.5, 34.0; IR (Neat): 3063, 3033, 2951, 1732, 1610, 1489, 1467, 1455, 1366, 1264, 1177; HRMS (ESI): calcd for [M+H]$^+$ ($C_{45}H_{40}O_8N$)$^+$ requires 722.2748; found 722.2754; enantiomeric excess: 45%, determined by HPLC (Chiralpak PC-2, hexane/*i*-PrOH 80/20, flow rate 1.0 mL/min; t_{major} = 25.6 min, t_{minor} = 37.1 min, λ = 254 nm).

*Dibenzyl-(1R,2S,5R)-1′-benzyl-2-cyano-5-(2-methoxy-2-oxoethyl)-2′ -oxospiro- [cyclopentane-1,3′-indoline]-3,3-dicarboxylate (**4wa**).* 58 mg, yield 90%; colorless oil; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.43 (dd, *J* = 1.2, 7.6 Hz, 2H), 7.15−7.25 (m, 16H), 6.97−7.01 (m, 1H), 6.71 (d, *J* = 7.6 Hz, 1H), 5.24 (d, *J* = 12.0 Hz, 1H), 5.09−5.18 (m, 2H), 5.01 (d, *J* = 12.4 Hz, 1H), 4.82−4.93 (m, 2H), 4.86 (s, 1H), 3.44 (s, 3H), 2.71−2.96 (m, 3H), 1.76−1.88 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 175.3, 171.0, 169.3, 168.1, 142.8, 135.1, 134.6, 134.3, 129.8, 129.0, 128.9, 128.7 (2C), 128.6 (2C), 128.5, 128.3, 127.9, 127.1, 125.8, 125.2, 123.4, 115.7, 110.0, 69.0, 68.9, 62.4, 60.8, 51.8, 44.5, 43.8, 43.7, 39.6, 33.9; IR (Neat): 3064, 3033, 2953, 2243, 1732, 1612, 1489, 1468, 1455, 1370, 1271, 1182; HRMS (ESI): calcd for [M+H]$^+$ ($C_{39}H_{35}O_7N_2$)$^+$ requires 643.2439; found 643.2444; enantiomeric excess: 34%, determined by HPLC (Chiralpak ADH, hexane/*i*-PrOH 75/25, flow rate 1.0 mL/min; t_{major} = 58.2 min, t_{minor} = 46.4 min, λ = 220 nm).

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*Triethyl-(1R,2S,6R)-1′-benzyl-6-(2-methoxy-2-oxoethyl)-2′-oxospiro[cyclohexane-1,3′-indoline]-2,3,3-tricarboxylate (**4af**).* 35 mg, yield 60%; colorless oil; ^{1}H NMR ($CDCl_3$, 400 MHz, dr =2:1) δ 7.31−7.35 (m, 3H, major + minor), 7.16−7.26 (m, 5H, major + minor), 7.03−7.13 (m, 2H, major + minor), 6.81−6.94 (m, 2H, major + minor), 6.75 (d, J = 8.0 Hz, 1H, major), 6.61 (d, J = 7.6 Hz, 0.5H, minor), 4.98 (d, J = 15.6 Hz, 1H, major), 4.89 (d, J = 15.6 Hz, 0.5H, minor), 4.76 (d, J = 15.2 Hz, 1H, major), 4.74 (d, J = 15.6 Hz, 0.5H, minor), 4.10−4.25 (m, 5H, major + minor), 4.01 (s, 1H, major), 3.86−3.92 (m, 2.5H, major + minor), 3.68−3.75 (m, 2H, major + minor), 3.49 (s, 3H, major), 3.42 (s, 1.5H, minor), 2.67−2.73 (m, 1.5H, major + minor), 2.40−2.46 (m, 1H, major), 2.27−2.32 (m, 0.5H, minor), 2.13−2.20 (m, 0.5H, minor), 1.99−2.07 (m, 1H, major), 1.79−1.94 (m, 2H, major + minor), 1.63−1.68 (m, 2H, major + minor), 1.22−1.30 (m, 4.6H, major + minor), 1.15 (t, J = 7.2 Hz, 2H, minor), 0.96 (t, J = 7.2 Hz, 3H, major), 0.95 (t, J = 7.2 Hz, 3H, major), 0.90 (t, J = 7.2 Hz, 2H, minor); ^{13}C NMR ($CDCl_3$, 100 MHz, dr =2:1) δ (major) 178.7, 172.0, 171.8, 170.0, 169.3, 144.2, 136.1, 132.0, 128.7, 128.2, 128.1, 128.0, 127.7, 127.6, 124.9, 121.5, 109.2, 62.1, 61.7, 60.8, 56.6, 53.0, 51.9, 51.6, 44.7, 41.1, 34.6, 32.0, 24.1, 14.0, 13.6, 13.4; (minor) 176.3, 172.5, 172.4, 169.2, 168.3, 144.3, 136.3, 128.6, 127.5, 122.5, 121.1, 108.5, 62.0, 61.3, 60.7, 56.9, 52.1, 44.2, 42.3, 34.5, 32.6, 22.6, 13.9, 13.7, 13.6; IR (Neat): 2981, 2936, 1739, 1715, 1610, 1490, 1466, 1369, 1251, 1201; HRMS (ESI): calcd for $[M+H]^+$ $(C_{32}H_{38}O_9N)^+$ requires 580.2541; found 580.2536; enantiomeric excess: 38%, determined by HPLC (Chiralpak ADH, hexane/*i*-PrOH 75/25, flow rate 1.0 mL/min; t_{major} = 31.9 min, t_{minor} = 22.7 min, λ = 254 nm).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b01553.

Cyrstallograpic data for **4ae** (CIF)

^{1}H and ^{13}C NMR spectra and HPLC traces (PDF)

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Notes

The authors declare no competing financial interest.

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