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Synthesis of Chiral Thiourea-Thioxanthone Hybrids

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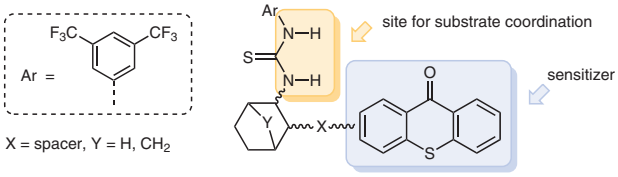

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Abstract Four different 1-aminocyclohexanes bearing a tethered thioxanthone group in the 2-position were prepared. The synthesis commenced with the respective N-protected β-amino acids, the carboxyl group of which was employed for the introduction of the thioxanthone moiety. After construction of the thioxanthone and protecting group removal, the conversion of the amino group into the respective thiourea was accomplished by treatment with *N*-3,5-bis(trifluoromethyl)phenyl isothiocyanate and yielded the title compounds in which the thioxanthone resides in different spatial positions relative to the thiourea motif. Overall yields varied between 20–35%.

Key words amino acids, chiral pool, esterification, indium, oxazoles, photochemistry, thiourea, thioxanthone

Thioxanthone (9*H*-thioxanthen-9-one) exhibits its longest wavelength absorption maximum at λ = 376 nm (ε = 6200 M^{-1} cm^{-1}) and its triplet energy has been determined as 265 kJ mol^{-1}.[1] The triplet state is populated by direct irradiation with a quantum yield of 0.85 in benzene[2] and thioxanthone has consequently been employed as a triplet sensitizer for several applications.[3] Recent interest in visible-light-induced enantioselective transformations[4] has led to the development of thioxanthone derivatives in which the chromophore is linked to a chiral backbone. In our group, the linkage was achieved via oxazole annulation to a chiral 1,5,7-trimethyl-3-azabicyclo[3.3.1]nonan-2-one scaffold. The chiral sensitizer was shown to catalyze inter- and intramolecular [2+2] photocycloaddition reactions in a highly enantioselective fashion.[5,6] The Xiao group developed a bifunctional photocatalyst for an enantioselective aerobic oxidation in which the thioxanthone unit is connected to chiral bisoxazoline complexes by a conformationally flexible ester linkage.[7]

In light of the spectacular success the thiourea binding motif has encountered in organocatalysis,[8,9] it seems tempting to employ it also in photochemistry to exert chemo- and stereoselectivity control. The group of Sivaguru showed that a thiourea, which is linked at position C2 to an axially chiral 2′-hydroxy-1,1′-binaphthyl, is an effective catalyst for the enantioselective (86–92% *ee*) intramolecular [2+2] photocycloaddition[10] of 4-alkenylcoumarins.[10,11] Three hydrogen bonding interactions were invoked to explain the stereochemical outcome and to account for the bathochromic absorption shift that is responsible for the selective excitation of the catalyst-substrate complex. In additional work, it was discovered that the racemic intermolecular [2+2] photocycloaddition of coumarins can be mediated by achiral thiourea catalysts.[12] The Beeler group developed a bisthiourea, which is capable of binding a cinnamate at each of its binding sites, and thus increases the regioselectivity of the cinnamate [2+2] photodimerization.[13]

The stoichiometric use of a chiral thiourea was found by our group to induce a notable enantioselectivity (75% *ee*) in the intramolecular thioxanthone-sensitized [2+2] photocycloaddition of a 2,3-dihydropyridone-5-carboxylate.[3g] In particular, the last result triggered synthetic efforts aiming at a covalent linkage between a chiral thiourea entity and a thioxanthone and we herein report on the synthesis of such thiourea-thioxanthone hybrids.

The choice of compounds depicted in Figure 1 was inspired by the idea to make a set of chiral 1,2-disubstituted cyclohexanes available in which the thiourea and the thioxanthone unit would be oriented in varying spatial arrangements. Compound **1** bears both units in equatorial positions of a cyclohexane chair while a boat conformation of the cyclohexane is enforced in compound **2** with the thioxanthone and thiourea both located in a pseudoequatorial (*exo*) position. In compound **3**, either thiourea or thioxanthone could be axially positioned with the other substituent being equatorial. Since there was evidence (vide infra) that the thioxanthone was equatorial in **3**, a fourth cyclohexane derivative **4** was designed in which the thioxanthone unit would definitely be axial but the thiourea equatorial. In all catalysts **1**–**4**, the aryl substituent was selected to be the privileged 3,5-bis(trifluoromethyl)phenyl group.[14]

Taking compound **1** as an example, a few retrosynthetic considerations are illustrated in Scheme 1. Primary amine **5** was chosen as an immediate precursor for the thiourea since it was expected that treatment with 3,5-bis(trifluoro-

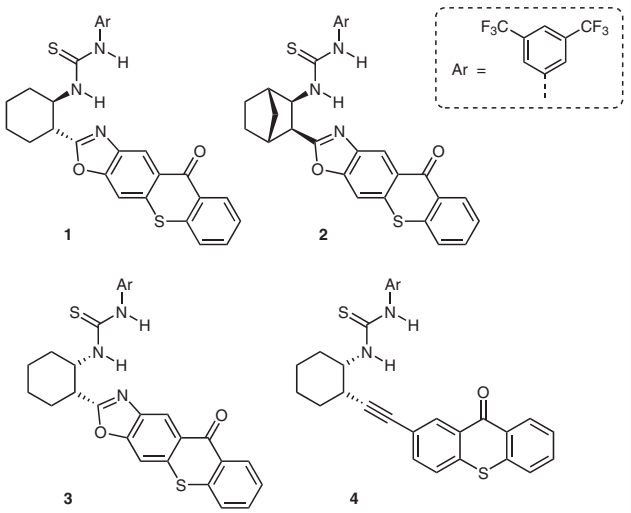
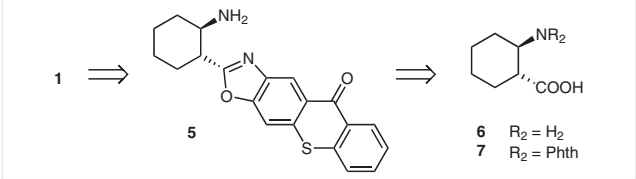


Figure 1 Structure of target compounds **1–4** in which a chiral thiourea is linked with a photochemically active thioxanthone via an annulated oxazole or an ethynyl group

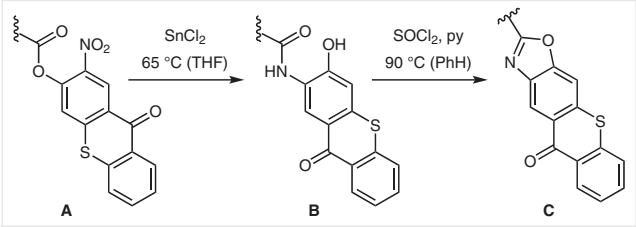
methyl)phenyl isothiocyanate[15] would not interfere with the thioxanthone functionality. In previous work on chiral templates and catalysts for enantioselective reactions, the oxazole group was identified as a reliable linker to be annulated to a given arene.[16] Formation of the oxazole requires a carboxylic acid precursor and it was expected that the amine group had to be protected prior to the annulation. The arene is normally introduced as its *ortho*-nitro-substituted aryl ester that upon reduction rearranges to the respective *ortho*-hydroxy-substituted amide (Scheme 2). For the desired thioxanthone annulation the starting material was thus 3-hydroxy-2-nitrothioxanthone,[5a] which was to be linked to an appropriately N-protected carboxylic acid derived from enantiopure compound **6**. Initial attempts to employ a benzyloxycarbonyl or *tert*-butyloxycarbonyl amine protecting group revealed that they were incompatible with the formation of the aryl ester bond or the subsequent reduction step. Likewise the immediate formation of the thiourea prior to the oxazole annulation was not viable. In most instances, not even the required ester **A** (Scheme 2) could be formed in useful yields. The phthaloyl protecting group (Phth) was thus selected as a putatively more robust protecting group with compound **7** being the desired starting material.

In previous work, the introduction of the thioxanthone had been achieved by reduction of the nitro group with tin(II) chloride in refluxing THF.[5a] The cyclization of amide **B** to the desired oxazole **C** was performed with thionyl chloride/pyridine (py) in refluxing benzene. When attempting to apply these conditions to the synthesis of N-substituted ester derivatives of acid **6**, there was either no reaction or the formation of decomposition products was observed. The most promising route was the immediate use of the respective thiourea with which a moderate yield of the respective ester **A** was achieved. The reduction could, however, not be performed.

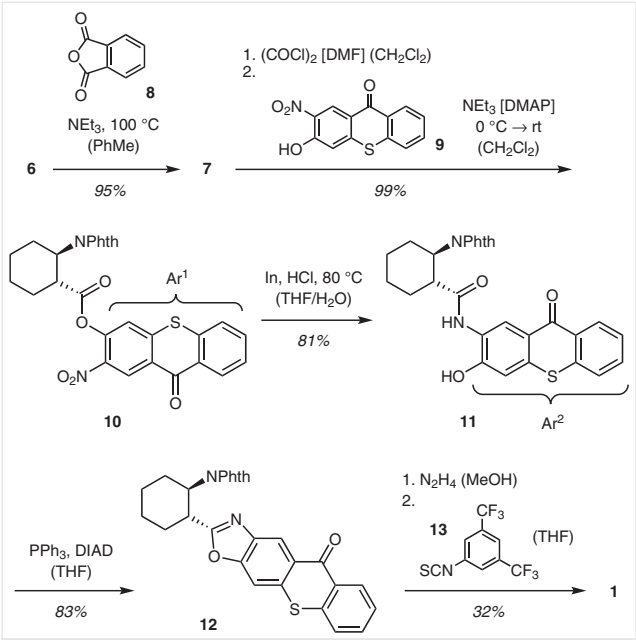
Similar issues were initially encountered with the *N*-phthaloyl derivative **7**, which was readily accessible from acid **6** by treatment with phthalic anhydride (**8**) and triethylamine in benzene (Scheme 3).[17] Ester formation proceeded smoothly after activation via the acid chloride and reaction with thioxanthone **9**.[5a] Attempted reduction of compound **10** with tin(II) chloride or by Pd-catalyzed transfer hydrogenation[18] remained unsuccessful. Gratifyingly, it



Scheme 1 Retrosynthetic considerations for the construction of thiourea-thioxanthone hybrids (Phth = phthaloyl)



Scheme 2 Synthetic access to oxazole-annulated thioxanthones **C** starting with (2-nitrothioxanthone-3-yl) ester **A**



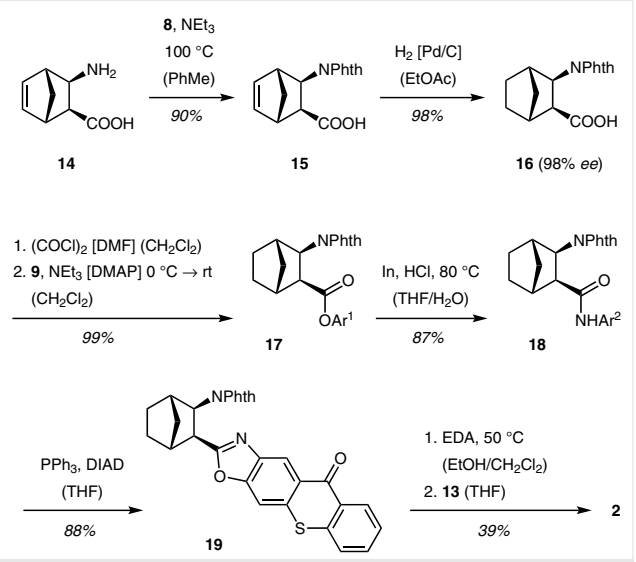
Scheme 3 Synthesis of thiourea-thioxanthone hybrid **1** starting from β-amino acid **6**

was found that the nitro group could be reduced smoothly with indium in an acidic THF/water mixture.[19] In the event, the acyl group underwent the expected O–N migration and amide **11** was isolated in 81% yield. The cyclization to the oxazole ring was achieved under Mitsunobu conditions[20] while the use of $SOCl_2$ and $POCl_3$ as dehydrating agents failed. Oxazole **12** was obtained in 83% yield and the removal of the phthaloyl protecting group was accomplished by hydrazinolysis.[21] Eventually, the desired thiourea was prepared by treatment of amine **5** with 3,5-bis(trifluoromethyl)phenyl isothiocyanate (**13**). The relatively low overall yield is likely due to material loss in the hydrazinolysis reaction (vide infra).

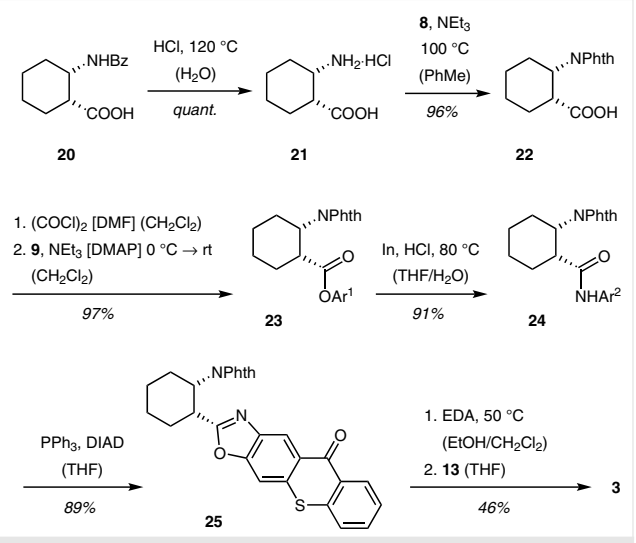
For the synthesis of compound **2**, access to enantiopure β-amino acid **14**[22] was required (Scheme 4). This goal was accomplished by applying a known enantiotopos-differentiating methanolysis reaction to the respective succinic anhydride.[23] Curtius rearrangement, reduction, and ester hydrolysis (100 °C in 1,4-dioxane/water) led to the desired compound, which was converted into the phthaloyl derivative **15** by treatment with phthalic anhydride. Hydrogenation of the endocyclic double bond furnished carboxylic acid **16**, the enantiomeric excess (*ee*) of which was determined by chiral HPLC analysis to be 98%. The remaining sequence followed the route developed for compound **1**. After formation of ester **17**, the reduction of the nitro arene with indium and the concomitant rearrangement led to amide **18**, which was further transformed under Mitsunobu conditions into thioxanthone **19**. In this instance, the attempted removal of the phthaloyl group by hydrazinolysis was not successful but led only to decomposition. Methylamine[24] led to the cleavage of one imide N–C bond but the reaction remained stalled at the stage of the amide. The best result was achieved by treating phthalimide **19** with ethylenediamine (EDA) at 50 °C.[25] The protecting group was completely removed and the resulting primary amine was immediately converted into the desired thiourea **2**.

While the thiourea and the thioxanthone are locked by the rigid norbornane ring in **2**, a conformationally more flexible *cis*-substitution at the cyclohexane ring was expected for thiourea **3**. The synthesis (Scheme 5) commenced with commercially available *N*-benzoyl (Bz)-protected amino acid **20**, which was converted via free acid hydrochloride **21**[26,27] into the *N*-phthaloyl-protected amino acid **22**. The subsequent sequence of esterification, reduction/rearrangement, and oxazole ring closure proved its reliability and efficiency by providing the respective intermediates **23**, **24**, and **25** in excellent yields (89–97%). Treatment with EDA turned out to be also in this case the preferred method for phthaloyl removal and delivered the primary amine for immediate conversion into thiourea **3**. The overall yield for the six-step synthesis was 35%.

The conformational preference of compound **3** was studied by ^{1}H NMR spectroscopy at ambient temperature.



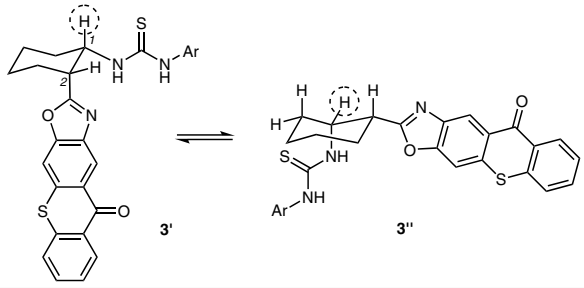
Scheme 4 Synthesis of thiourea-thioxanthone hybrid **2** starting from β-amino acid **14**



Scheme 5 Synthesis of thiourea-thioxanthone hybrid **3** starting from *N*-benzoyl-protected β-amino acid **20**

The proton at carbon atom C1 (Scheme 6) is expected to exhibit in conformation **3′** one large coupling constant due to the axial-axial coupling ($^3J_{aa}$) and two small coupling constants due the axial-equatorial coupling ($^3J_{ae}$).[28] Indeed, its precursor **25** showed exactly this pattern with $^3J_{aa}$ = 13.2 Hz and $^3J_{ae}$ = 5.2 Hz and $^3J_{ae}$ = 3.6 Hz. The proton at C2 appeared as a virtual quartet with an average coupling constant of ^3J ≅ 5.2 Hz. Related ^{1}H NMR data were recorded for compounds **23** and **24**. However, the situation was different for compound **3**. The ^{1}H NMR spectrum revealed for H1 a signal that appeared as virtual tt with two coupling constants of ^3J

≅ 8.3 Hz and ^3J ≅ 4.0 Hz. While one of the larger signal splittings is due to the coupling to NH, the remaining coupling pattern (^3J = 8.3, 4.0, 4.0 Hz) results from coupling to vicinal protons. Likewise, the proton H2 changed its signal pattern and appeared as a virtual dt with ^3J = 7.4 Hz and ^3J ≅ 4.3 Hz.

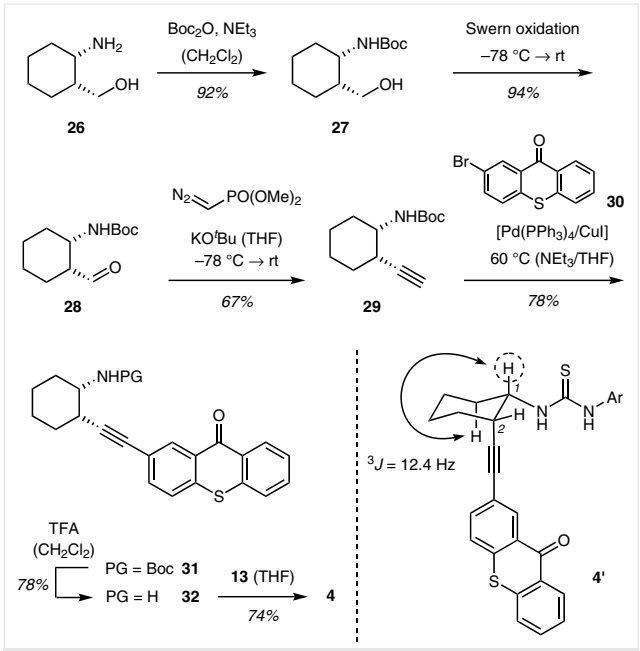


Scheme 6 Equilibrium between conformations **3′** and **3′′** of compound **3** as suggested by the ^{1}H NMR data for the indicated proton (see narrative)

Apparently there is no clear preference for either conformer **3′** or **3″** and neither proton H1 nor H2 has a clear preference for the axial position. Rather it seems as if an equilibrium was established at ambient temperature most likely due to the fact that the two substituents at C1 and C2 are similar in size. In order to establish a less ambiguous conformational situation within the *cis*-substituted cyclohexane ring, a thiourea-thioxanthone hybrid **4** was devised in which the thioxanthone was linked to the cyclohexane ring by the linear, sterically unencumbered[29] ethynyl group. The synthesis of this compound started from hydrochloride **21**, which was reduced with $LiAlH_4$ in THF to furnish amino alcohol **26** in 93% yield (Scheme 7). Upon *tert*-butoxycarbonyl (Boc) protection of the amino group, alcohol **27**[30] was subjected to a Swern oxidation.[31] The resulting aldehyde **28** was converted into the terminal alkyne **29** by Seyferth–Gilbert homologization.[32] Sonogashira cross-coupling[33] with the known 2-bromothioxanthone (**30**)[34] gave the 2-substituted thioxanthone **31**, which could be readily deprotected with trifluoroacetic acid (TFA) to give the desired amine **32**. As in the previous syntheses, the desired thiourea was generated by treatment of the amine with 3,5-bis(trifluoromethyl)phenyl isothiocyanate (**13**).

As expected, compound **4** displays preferred conformation **4′** in which the tethered thioxanthone is axially positioned. The ^{1}H NMR coupling pattern of proton H1 is a virtual ddt with coupling constants of ^3J = 12.4 Hz, ^3J = 8.5 Hz, and ^3J ≅ 3.9 Hz. Since the coupling constant of ^3J = 8.5 Hz could be clearly assigned to the vicinal CH–NH coupling the other coupling constants are due to vicinal CH–CH coupling with $^3J_{aa}$ = 12.4 Hz and $^3J_{ae}$ ≅ 3.9 Hz. Likewise, the equatorial proton H2 shows a virtual quartet with the $^3J_{ae}$ ≅ $^3J_{ee}$ = 3.6 Hz.

The UV/Vis spectra of the new thioxanthones are all similar (see the Supporting Information) and the spectrum



Scheme 7 Preferred conformation **4′** and synthesis of thiourea-thioxanthone hybrid **4** starting from β-amino alcohol **26**

of compound **4** is representatively shown in Figure 2. The long-wavelength absorption between 370 and 420 nm with a λ_{max} = 392 nm (ε = 3340 M^{-1} cm^{-1}) is likely due to the thioxanthone chromophore while the strong absorptions setting in below 320 nm are attributed to allowed transitions of the thiourea and the thioxanthone. In line with their UV/Vis spectra, the compounds are yellow-colored solids. Phosphorescence data have not yet been obtained but it was expected that the compounds will act as triplet sensitizers in the same fashion as does the parent thioxanthone.

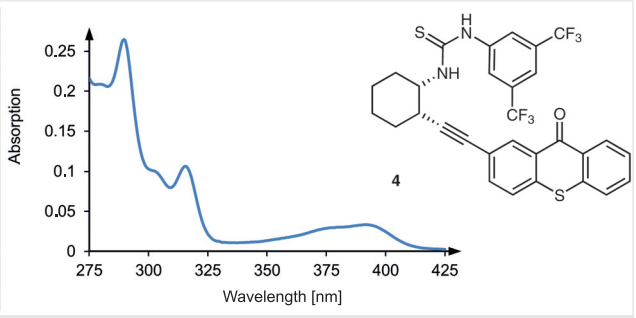
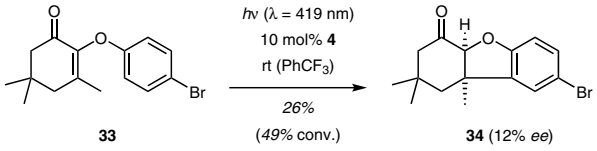


Figure 2 UV/Vis spectrum of thiourea-thioxanthone hybrid **4** in CH_2Cl_2 solution (*c* = 0.1 mM)

In preliminary and non-optimized experiments, it was probed whether the thiourea-thioxanthone hybrids would act as catalysts of visible-light-induced reactions. Along these lines, catalyst **4** was employed in the photocyclization of 2-aryloxycyclohex-2-enones,[35] which has recently

received increasing attention.[3h,36] Gratifyingly, we found that the reaction of compound **33**, which does not proceed at λ = 419 nm in the absence of a sensitizer could be successfully promoted by catalyst **4** (Scheme 8). Although the yield and enantioselectivity of product **34** was low, the experiment demonstrates that the thiourea-thioxanthone hybrids are catalytically active and that an asymmetric binding event at the NH-hydrogen atoms of the thiourea is likely to occur.



Scheme 8 Sensitized photocyclization of 2-(4-bromophenoxy)-3,5,5-trimethylcyclohex-2-enone (**33**)

In summary, we have successfully synthesized four thiourea-thioxanthone hybrid compounds from the respective β-amino acids. For the attachment of the thioxanthone by oxazole annulation we have devised a generally applicable and mild reaction sequence. The compounds exhibit a two-point hydrogen bonding site at the thiourea and it is expected that the thioxanthone will act as a sensitizer to promote photochemical reactions of bound substrates in the respective 1:1 complexes. Work along these lines is currently underway in our laboratories and will be reported in due course.

All reactions involving moisture-sensitive chemicals were carried out in flame-dried glassware under positive pressure of argon with magnetic stirring. THF, CH_2Cl_2, and Et_2O were purified using a SPS-800 solvent purification system (M. Braun). TLC was performed on silica-coated glass plates (silica gel 60 F^{254}) with detection by UV (λ = 254 nm), cerium ammonium molybdate (CAM) or $KMnO_4$ (0.5% in H_2O) with subsequent heating. Flash chromatography was performed on silica gel 60 (Merck, 230–400 mesh) with the indicated eluent. Common solvents for chromatography [pentane (Pn), cyclohexane (Chx), EtOAc, CH_2Cl_2, Et_2O, MeOH] were distilled prior to use. Solutions refer to sat. aq solutions, unless otherwise stated. IR spectra were recorded on a JASCO IR-4100 (ATR). MS/HRMS measurements were performed on a Finnigan MAT 8200 or Thermo Fisher DFS (EI)/Finnigan LSQ classic or Thermo Fisher LTY Orbitrap XL (ESI). ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ or DMSO-d_6 at 300 K on a Bruker AV-360, Bruker AVHD-400, Bruker AV-500, or a Bruker AVHD-500 instrument. Chemical shifts are reported relative to $CHCl_3$ (δ = 7.26) or DMSO-d_5 (δ = 2.50). Apparent multiplets that occur as a result of the accidental equality of coupling constants to those of magnetically non-equivalent protons are marked as virtual (virt.). The multiplicities of the ^{13}C NMR signals were determined by DEPT-edited phase sensitive HSQC experiments. Assignments are based on COSY, HMBC, HSQC, and NOESY experiments. Signals that could not be assigned unambiguously are marked with an asterisk (*). UV/Vis Spectroscopy was performed on a PerkinElmer Lambda 35 UV/Vis spektometer. Unless otherwise mentioned, UV spectra were recorded using a Hellma precision cell made of quartz with a pathway of 1 mm. Solvents and concentrations are given for each spectrum. Rotation value measurements were performed on a Bellingham + Stanley ADP400+ with a 0.05 dm cuvette at λ = 589 nm (Na D-line) at room temperature. The specific rotation is given in 10^{-1} grad cm^2 g^{-1}, the concentration is given in g/100 mL. Analytical HPLC was performed using a chiral stationary phase (flow rate: 1.0 mL/min, column type and eluent are given for the corresponding compounds) and UV detection (λ = 210 nm or 254 nm) at 20 °C.

(1*R*,2*R*)-2-(1′,3′-Dioxoisoindolin-2′-yl)cyclohexane-1-carboxylic Acid (7)

Amino acid **6** (200 mg, 1.40 mmol, 1.00 equiv) was dissolved in anhyd toluene (20 mL). Subsequently, phthalic anhydride (218 mg, 1.47 mmol, 1.05 equiv) and NEt_3 (283 mg, 0.38 mL, 2.80 mmol, 2.00 equiv) were added. The mixture was stirred at 100 °C. After 18 h, the solution was cooled to rt and washed with aq 3 M HCl (100 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were dried (Na_2SO_4), filtered and the solvent was removed under reduced pressure. The desired product was obtained as a colorless solid (363 mg, 1.33 mmol, 95%) and was used in the next step without purification; mp 138–140 °C; $[\alpha]_D^{20}$ –10 (*c* = 1.00, CH_2Cl_2).

IR (ATR): 3514 (m, OH), 3369 (w, OH), 2936 (m, CH_{sp3}), 2861 (m, CH_{sp3}), 1740 (m), 1697 (s, C=O), 1376 (m), 1330 (m), 1204 (w), 1077 (m), 718 cm^{-1} (m).

^1H NMR (400 MHz, $CDCl_3$): δ = 1.28–1.60 (m, 3 H, H-5, H-6), 1.69–1.90 (m, 3 H, H-3, H-4), 1.99–2.20 (m, 2 H, H-3, H-6), 3.43 (virt. td, $^3J \cong {}^3J$ = 12.1 Hz, ^3J = 3.7 Hz, 1 H, H-1), 4.28 (ddd, ^3J = 12.1, 11.3, 4.0 Hz, 1 H, H-2), 7.67 (dd, ^3J = 5.5 Hz, ^4J = 3.0 Hz, 2 H, H-5′, H-6′), 7.78 (dd, ^3J = 5.5 Hz, ^4J = 3.0 Hz, 2 H, H-4′, H-7′), 10.40 (br s, 1 H, OH).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 24.7 (t, C-5), 25.3 (t, C-4), 29.7 (t, C-6), 29.8 (t, C-3), 44.7 (d, C-1), 51.0 (d, C-2), 123.4 (d, 2 C, C-4′, C-7′), 131.9 (s, 2 C, C-3a′, C-7a′), 134.0 (d, 2 C, C-5′, C-6′), 168.2 (s, 2 C, C-1′, C-3′), 179.2 (s, COOH).

MS (EI, 70 eV): *m*/*z* (%) = 273 (8, $[M]^+$), 227 (12, $[M - CH_3]^+$), 186 (15), 160 (63), 148 (20, $[C_8H_6NO_2]^+$), 91 (100, $[C_7H_7]^+$).

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{15}H_{15}NO_4$: 273.1001; found: 273.0996.

2′-Nitro-9′-oxo-9′*H*-thioxanthen-3′-yl (1*R*,2*R*)-2-(1″,3″-Dioxoisoindolin-2″-yl)cyclohexane-1-carboxylate (10)

The protected amino acid **7** (666 mg, 2.34 mmol, 1.10 equiv) was dissolved in anhyd CH_2Cl_2 (33 mL). Oxalyl chloride (297 mg, 0.20 mL, 2.34 mmol, 1.10 equiv) and a catalytic amount of DMF (7 drops) was added at rt. The mixture was stirred at rt for 3 h. In parallel, thioxanthone **9** (581 mg, 2.13 mmol, 1.00 equiv) and a catalytic amount of 4-dimethylaminopyridine (10 crystals) was dissolved in anhyd CH_2Cl_2 (33 mL) and cooled to 0 °C. At this temperature, NEt_3 (647 mg, 0.89 mL, 6.39 mmol, 3.00 equiv) was added. Subsequently, the previously prepared solution of acid chloride was added slowly. The mixture was warmed to rt and stirred overnight. After 18 h, aq NH_4Cl (100 mL) was added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 150 mL) and the combined organic layers were washed with aq 2 M NaOH (200 mL), dried (Na_2SO_4), and filtered. The solvent was evaporated and the desired product was obtained without further purification as a yellowish solid (1.11 g, 2.11 mmol, 99%); mp 202–205 °C; R_f = 0.89 (CH_2Cl_2/MeOH 98:2) [UV, $KMnO_4$]; $[\alpha]_D^{20}$ –92 (*c* = 1.00, CH_2Cl_2).

IR (ATR): 3086 (w, CH_{sp2}), 3036 (w, CH_{sp2}), 2933 (m, CH_{sp3}), 2864 (m, CH_{sp3}), 1766 (s, C=O), 1708 (s, C=O), 1635 (s), 1605 (s), 1519 (m, $C{=}C_{sp2}$), 1379 (m), 1341 (s), 1293 (m), 1108 (m), 1077 (m), 1025 (m), 717 cm^{-1} (m).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.50–1.56 (m, 2 H, H-4, H-5), 1.78 (virt. td, $^3J \cong {}^3J$ = 12.8 Hz, ^3J = 3.4 Hz, 1 H, H-4), 1.90–1.99 (m, 3 H, H-3, H-5, H-6), 2.30 (virt. qd, $^3J \cong {}^3J$ = 12.4 Hz, ^3J = 2.8 Hz, 1 H, H-6), 2.49 (virt. td, $^3J \cong {}^3J$ = 13.7 Hz, ^3J = 1.8 Hz, 1 H, H-3), 3.84 (ddd, ^3J = 12.3 Hz, 11.3 Hz, 3.7 Hz, 1 H, H-1), 4.55 (ddd, ^3J = 12.3 Hz, 11.3 Hz, 4.0 Hz, 1 H, H-2), 7.17 (s, 1 H, H-4′), 7.54–7.58 (m, 2 H, H-5′, H-7′), 7.69 (ddd, ^3J = 8.3, 7.0 Hz, ^4J = 1.6 Hz, 1 H, H-6′), 7.74 (dd, ^3J = 5.5 Hz, ^4J = 3.1 Hz, 2 H, H-5″, H-6″), 7.87 (dd, ^3J = 5.5 Hz, ^4J = 3.1 Hz, 2 H, H-4″, H-7″), 8.54–8.60 (m, 1 H, H-8′), 9.20 (s, 1 H, H-1′).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.6 (t, C-4), 25.4 (t, C-5), 29.5 (t, C-6), 29.6 (t, C-3), 45.4 (d, C-1), 51.1 (d, C-2), 122.0 (d, C-4′), 123.4 (d, 2 C, C-4″, C-7″), 126.3 (d, C-5′), 127.1 (s, C-9a′), 127.8 (d, C-7′), 128.3 (d, C-1′), 128.5 (s, C-8a′), 130.3 (d, C-8′), 132.0 (s, 2 C, C-3a″, 7a″), 133.4 (d, C-6′), 134.2 (d, 2 C, C-5″, C-6″), 135.7 (s, C-4b′), 140.2 (s, C-3′), 144.1 (s, C-4a′), 145.9 (s, C-2′), 168.3 (s, 2 C, C-1″, C-3″), 170.9 (s, COO), 177.9 (s, C-9′).

MS (EI, 70 eV): *m*/*z* (%) = 528 (3, $[M]^+$), 273 (29, $[C_{13}H_7NO_4S]^+$), 256 (100, $[C_{15}H_{14}NO_3]^+$), 148 (79, $[C_8H_6NO_2]^+$).

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{28}H_{20}N_2O_7S$: 528.0991; found: 528.0995.

(1*R*,2*R*)-2-(1″,3″-Dioxoisoindolin-2″-yl)-*N*-(3′-hydroxy-9′-oxo-9′*H*-thioxanthen-2′-yl)cyclohexane-1-carboxamide (11)

Ester **10** (406 mg, 768 µmol, 1.00 equiv) was dissolved in THF (27 mL) and H_2O (27 mL) was added. To this solution In (441 mg, 3.84 mmol, 5.00 equiv) and concd HCl (0.75 mL) were added. The mixture was stirred at 80 °C for 18 h. After this time, the solution was cooled to rt and CH_2Cl_2 (50 mL) was added. The mixture was filtered over Celite and washed with aq $NaHCO_3$ (100 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were dried (Na_2SO_4), filtered, and the solvent was removed under reduced pressure. Purification by flash chromatography (4 × 20 cm, CH_2Cl_2/MeOH 95:5) furnished the title compound as an orange-colored solid (310 mg, 622 µmol, 81%); mp 150–154 °C; R_f = 0.51 (CH_2Cl_2/MeOH 95:5) [UV, $KMnO_4$]; $[\alpha]_D^{20}$ +46 (*c* = 1.00, CH_2Cl_2).

IR (ATR): 3296 (w, NH), 3066 (w, OH), 2931 (m, CH_{sp3}), 2857 (m, CH_{sp3}), 1766 (w), 1700 (s, C=O), 1588 (m, $C{=}C_{sp2}$), 1517 (m, $C{=}C_{sp2}$), 1438 (m, CH_{sp3}), 1369 (m), 1294 (w), 1262 (w), 1077 (m), 717 cm^{-1} (m, CH_{sp2}).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.00–1.17 (m, 1 H, H-5), 1.42–1.54 (m, 1 H, H-4), 1.63–1.82 (m, 4 H, H-3, H-4, H-5, H-6), 2.00 (virt. dq, ^3J = 12.7 Hz, $^3J \cong {}^3J$ = 3.6 Hz, 1 H, H-3), 2.06–2.18 (m, 1 H, H-6), 3.82 (virt. td, $^3J \cong {}^3J$ = 11.8 Hz, ^3J = 3.7 Hz, 1 H, H-1), 4.53 (virt. td, $^3J \cong {}^3J$ = 11.8 Hz, ^3J = 4.0 Hz, 1 H, H-2), 6.99 (s, 1 H, H-4′), 7.44–7.48 (m, 2 H, H-7′, H-5′), 7.53–7.56 (m, 1 H, H-6′), 7.59 (dd, ^3J = 5.5 Hz, ^4J = 3.0 Hz, 2 H, H-5″, H-6″), 7.73 (dd, ^3J = 5.5 Hz, ^4J = 3.0 Hz, 2 H, H-4″, H-7″), 8.47 (s, 1 H, H-1′), 8.61 (dd, ^3J = 8.4 Hz, ^4J = 1.6 Hz, 1 H, H-8′), 9.33 (s, 1 H, NH), 10.81 (s, 1 H, OH).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 24.7 (t, C-5), 25.2 (t, C-4), 29.8 (t, C-3), 30.9 (t, C-6), 47.4 (d, C-1), 51.8 (d, C-2), 114.6 (d, C-4′), 121.9 (s, C-4a′), 123.4 (d, 2 C, C-4″, C-7″), 123.7 (d, C-1′), 126.0 (d, C-7′), 126.4 (d, C-5′), 126.9 (s, C-3′), 128.6 (s, C-8a′), 130.0 (d, C-8′), 131.8 (s, 2 C, C-3a″, C-7a″), 132.2 (d, C-6′), 134.1 (d, 2 C, C-5″, C-6″), 136.6 (s, C-9a′), 137.5 (s, C-4b′), 153.8 (s, C-2′), 168.5 (s, 2 C, C-1″, C-3″), 175.2 (s, CON), 179.3 (s, C-9′).

MS (EI, 70 eV): *m*/*z* (%) = 498 (1, $[M]^+$), 480 (10 $[M - H_2O]^+$), 333 (100, $[C_{20}H_{15}NO_2S]^+$), 280 (10), 170 (3), 71 (10).

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{28}H_{22}N_2O_5S$: 498.1249; found: 498.1248.

2-{(1*R*,2*R*)-2-(10′-Oxo-10′*H*-thioxantheno[2′,3′-*d*]oxazol-2′-yl)-cyclohexyl}isoindoline-1″,3″-dione (12)

The synthesized amide **11** (275 mg, 552 µmol, 1.00 equiv) was dissolved in anhyd THF (26 mL). At rt, PPh_3 (318 mg, 1.21 mmol, 2.20 equiv) and diisopropyl azodicarboxylate (245 mg, 0.24 mL, 1.21 mmol, 2.20 equiv) were added. The mixture was stirred at rt and after 4 h, the solvent was evaporated. The crude product was purified by flash chromatography (4 × 25 cm, CH_2Cl_2/MeOH 98:2). The desired product was obtained as a yellow solid (220 mg, 458 µmol, 83%); mp 225–227 °C; R_f = 0.50 (CH_2Cl_2/MeOH 98:2) [UV, $KMnO_4$]; $[\alpha]_D^{20}$ –152 (*c* = 1.00, CH_2Cl_2).

IR (ATR): 3071 (w, CH_{sp2}), 2952 (m, CH_{sp3}), 2921 (m, CH_{sp3}), 2864 (w, CH_{sp3}), 1764 (m, C=O), 1701 (s, C=O), 1643 (m), 1620 (s), 1435 (m, CH_{sp3}), 1394 (m), 1373 (m), 1293 (m), 1244 (w), 1155 (w), 1077 (m), 1023 (m), 719 cm^{-1} (m, CH_{sp2}).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.49–1.65 (m, 2 H, H-4, H-5), 1.82–2.07 (m, 4 H, H-3, H-4, H-5, H-6), 2.29–2.45 (m, 2 H, H-3, H-6), 4.12 (ddd, ^3J = 12.3 Hz, 11.4 Hz, 3.6 Hz, 1 H, H-2), 4.57 (virt. td, $^3J \cong {}^3J$ = 11.7 Hz, ^3J = 3.8 Hz, 1 H, H-1), 7.44 (ddd, ^3J = 8.2 Hz, 6.9 Hz, ^4J = 1.3 Hz, 1 H, H-8′), 7.48–7.52 (m, 2 H, H-4′, H-6′), 7.57 (ddd, ^3J = 8.3 Hz, 6.9 Hz, ^4J = 1.5 Hz, 1 H, H-7′), 7.64 (dd, ^3J = 5.5 Hz, ^4J = 3.0 Hz, 2 H, H-5″, H-6″), 7.74 (dd, ^3J = 5.5 Hz, ^4J = 3.0 Hz, 2 H, H-4″, H-7″), 8.55 (dd, ^3J = 8.2 Hz, ^4J = 1.5 Hz, 1 H, H-9′), 8.76 (s, 1 H, H-11′).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 24.8 (t, C-4), 25.5 (t, C-5), 29.9 (t, C-3), 30.7 (t, C-6), 40.0 (d, C-2), 52.5 (d, C-1), 106.3 (d, C-4′), 122.0 (d, C-11′), 123.4 (d, 2 C, C-4″, C-7″), 125.7 (d, C-6′), 126.4 (d, C-8′), 126.5 (s, C-4a′), 128.7 (s, C-9a′), 130.0 (d, C-9′), 131.8 (s, 2 C, C-3a″, C-7a″), 132.3 (d, C-7′), 134.1 (d, 2 C, C-5″, C-6″), 134.2 (s, C-10a′), 137.0 (s, C-5a′), 141.0 (s, C-3a′), 153.0 (s, C-11a′), 168.2 (s, 2 C, C-1″, C-3″), 168.9 (s, C-2′), 179.8 (s, C-10′).

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{28}H_{20}N_2O_4S$: 481.1217; found: 481.1217.

1-[3″,5″-Bis(trifluoromethyl)phenyl]-3-{(1*R*,2*R*)-2-(10′-oxo-10′*H*-thioxantheno[2′,3′-*d*]oxazol-2′-yl)cyclohexyl}thiourea (1)

Oxazole **12** (70.0 mg, 146 µmol, 1.00 equiv) was dissolved in anhyd MeOH (13 mL). Hydrazine hydrate (364 mg, 0.36 mL, 7.29 mmol, 50.0 equiv) was added and the mixture was stirred at rt for 24 h. Upon removal of the solvent, the residue was dissolved in CH_2Cl_2 and filtered over SiO_2 (1 × 2 cm, CH_2Cl_2/MeOH 95:5). After evaporation of the solvent, the crude material was used in the next step without further purification. The crude material was dissolved in anhyd THF (10 mL) and 3,5-bis(trifluoromethyl)phenyl isothiocyanate (83.1 mg, 0.06 mL, 307 µmol, 2.10 equiv) was added. The reaction mixture was stirred at rt and after 18 h, the solvent was evaporated. Purification by flash chromatography (2 × 7 cm, CH_2Cl_2/MeOH 99:1) afforded the desired thiourea as a yellow solid (29.0 mg, 46.7 µmol, 32% over two steps); mp 124–126 °C; R_f = 0.20 (CH_2Cl_2/MeOH 99:1) [UV, $KMnO_4$]; $[\alpha]_D^{20}$ +80 (*c* = 1.00, CH_2Cl_2).

IR (ATR): 3327 (w, NH), 2956 (w, CH_{sp3}), 2929 (w, CH_{sp3}), 2852 (w, CH_{sp3}), 1701 (m, C=O), 1625 (m, $C{=}C_{sp2}$), 1438 (m, CH_{sp3}), 1277 (m), 1028 (m), 910 (m), 749 cm^{-1} (m, CH_{sp2}).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.55–1.79 (m, 4 H, H-4, H-5), 1.93–2.00 (m, 2 H, H-3, H-6), 2.08–2.17 (m, 1 H, H-6), 2.37–2.41 (m, 1 H, H-3), 3.73 (br s 1 H, H-2), 4.96–5.16 (m, 1 H, H-1), 7.41–7.68 (m, 5 H, H-4′, H-6′, H-7′, H-8′, H-4″), 7.95 (s, 2 H, H-2″), 8.15 (br s, 1 H, NH), 8.50 (d, ^3J = 8.1 Hz, 1 H, H-9′), 8.68 (s, 1 H, H-11′), 9.01 (br s, 1 H, NH).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 21.2 (t, C-4*), 22.0 (t, C-5*), 28.3 (t, C-6), 39.3 (t, C-3), 54.0 (d, C-2), 60.6 (d, C-1), 106.8 (d, C-4′), 118.7 (d, C-4″), 119.0 (s, C-1″), 121.3 (d, C-11′), 122.5 (q, $^1J_{C,F}$ = 165 Hz, 2 C, CF_3),

123.8 (d, 2 C, C-2″), 125.9 (d, C-6′*), 126.3 (d, C-7′*), 128.2 (s, C-4a′), 129.9 (d, C-8′), 132.4 (q, ^2J = 33.6 Hz, 2 C, C-3″), 132.8 (d, C-9′), 134.9 (s, C-9a′), 137.4 (s, C-5a′), 139.9 (s, C-10a′), 140.0 (s, C-3a′), 152.5 (s, C-11a′), 169.3 (s, C-2′), 180.0 (s, C-10′), 180.3 (s, NCSN).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{29}H_{21}F_6N_3O_2S_2$: 622.1052; found: 622.1047.

(1*S*,2*S*,3*R*,4*R*)-3-(1′,3′-Dioxoisoindolin-2′-yl)bicyclo[2.2.1]hept-5-ene-2-carboxylic Acid (15)

Amino acid **14** (962 mg, 6.28 mmol, 1.00 equiv) was dissolved in anhyd toluene (150 mL). Subsequently, phthalic anhydride (978 mg, 6.60 mmol, 1.05 equiv) and NEt_3 (1.26 g, 1.74 mL, 12.6 mmol, 2.00 equiv) were added. The mixture was stirred at 100 °C. After 18 h, the solution was cooled to rt and washed with aq 3 M HCl (150 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 150 mL). The combined organic layers were dried (Na_2SO_4), filtered, and the solvent was removed under reduced pressure. The desired product was obtained as a brown viscous oil (1.60 g, 5.65 mmol, 90%); $[\alpha]_D^{20}$ +64 (*c* = 1.00, CH_2Cl_2).

IR (ATR): 3227 (m, OH), 3059 (w, CH_{sp2}), 2983 (w, CH_{sp3}), 2952 (w, CH_{sp3}), 1770 (m), 1703 (s, C=O), 1402 (m), 1367 (s), 1329 (s), 1178 (m), 1158 (m), 872 (m), 714 (s), 695 (s), 662 cm^{-1} (m).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.75 (virt. dt, ^2J = 9.3 Hz, $^3J \cong {}^3J$ = 1.9 Hz, 1 H, H-7), 2.63 (virt. dt, ^2J = 9.3 Hz, $^3J \cong {}^3J$ = 1.9 Hz, 1 H, H-7), 2.77 (dd, ^3J = 8.6 Hz, ^4J = 1.8 Hz, 1 H, H-2), 3.18 (virt. t, $^3J \cong {}^3J$ = 1.9 Hz, 1 H, H-4), 3.42 (d, ^3J = 1.9 Hz, 1 H, H-1), 4.28 (dd, ^3J = 8.6 Hz, ^4J = 1.8 Hz, 1 H, H-3), 6.22 (dd, ^3J = 5.6 Hz, ^3J = 2.9 Hz, 1 H, H-6), 6.31 (dd, ^3J = 5.6 Hz, ^3J = 3.1 Hz, 1 H, H-5), 7.64–7.70 (m, 2 H, H-5′, H-6′), 7.74–7.81 (m, 2 H, H-4′, H-7′).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 45.3 (d, C-1), 45.6 (d, C-2), 45.9 (d, C-4), 47.8 (t, C-7), 55.6 (d, C-3), 123.2 (d, 2 C, C-4′, C-7′), 132.0 (s, 2 C, C-3a′, C-7a′), 134.0 (d, 2 C, C-5′, C-6′), 138.3 (d, C-5), 138.8 (d, C-6), 168.9 (s, 2 C, C-1′, C-3′), 176.9 (s, COOH).

MS (EI, 70 eV): *m*/*z* (%) = 92 (60, $[C_7H_8]^+$), 91 (100), 65 (13), 40 (12, $[C_3H_4]^+$).

HRMS (EI): *m*/*z* [M]$^+$ calcd for $C_{16}H_{13}NO_4$: 283.0845; found: 283.0836.

(1*R*,2*S*,3*R*,4*S*)-3-(1′,3′-Dioxoisoindolin-2′-yl)bicyclo[2.2.1]heptane-2-carboxylic Acid (16)

The protected amino acid **15** (1.53 g, 5.42 mmol, 1.00 equiv) was dissolved in EtOAc (92 mL) and Pd/C (10% w/w, 181 mg) was added. The mixture was stirred under H_2 atmosphere (balloon) at rt. After 18 h, the mixture was filtered over Celite and washed with CH_2Cl_2 (150 mL). The solvent was evaporated under reduced pressure. The product was isolated as a colorless solid (1.51 g, 5.31 mmol, 98%); mp 75–78 °C; $[\alpha]_D^{20}$ +36 (*c* = 1.00, CH_2Cl_2).

Chiral HPLC (OD-RH, 150 × 4.6 mm, MeCN/H_2O (2:10), 1 mL/min, λ = 210 nm, 254 nm): t_{R1} = 11.1 min, t_{R2} = 12.9 min.

IR (ATR): 3258 (m, OH), 2959 (m, CH_{sp3}), 2874 (m, CH_{sp3}), 1731 (s, C=O), 1453 (w), 1373 (w), 1286 (m), 1107 (m), 1073 (w), 719 cm^{-1} (s).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.24–1.38 (m, 3 H, H-5$_{ax}$, H-6$_{ax}$, H-7), 1.60–1.71 (m, 2 H, H-5$_{eq}$, H-6$_{eq}$), 2.61 (virt. dt, ^2J = 10.8 Hz, $^3J \cong {}^3J$ = 2.1 Hz, 1 H, H-7), 2.67 (d, ^3J = 3.7 Hz, 1 H, H-1*), 2.77 (d, ^3J = 3.4 Hz, 1 H, H-4*), 2.86 (dd, ^3J = 9.3 Hz, ^4J = 1.7 Hz, 1 H, H-2), 4.38 (dd, ^3J = 9.3 Hz, ^4J = 1.5 Hz, 1 H, H-3), 7.69 (dd, ^3J = 5.5 Hz, ^4J = 3.0 Hz, 2 H, H-5′, H-6′), 7.80 (dd, ^3J = 5.5 Hz, ^4J = 3.0 Hz, 2 H, H-4′, H-7′).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 28.0 (t, C-6), 29.8 (t, C-5), 37.8 (t, C-7), 40.1 (d, C-1*), 40.2 (d, C-4*), 53.1 (d, C-2), 57.5 (d, C-3), 123.3 (d, 2 C, C-4′, C-7′), 132.0 (s, 2 C, C-3a′, C-7a′), 134.0 (d, 2 C, C-5′, C-6′), 168.7 (s, 2 C, C-1′, C-3′), 175.1 (s, COOH).

MS (EI, 70 eV): *m*/*z* (%) = 185 (1, [M]$^+$), 94 (21), 78 (9), 66 (100), 40 (10).

HRMS (EI): *m*/*z* [M]$^+$ calcd for $C_{16}H_{15}NO_4$: 285.0996; found: 285.1000.

2′-Nitro-9′-oxo-9′*H*-thioxanthen-3′-yl (1*R*,2*S*,3*R*,4*S*)-3-(1″,3″-Dioxoisoindolin-2″-yl)bicyclo[2.2.1]heptane-2-carboxylate (17)

The protected amino acid **16** (870 mg, 3.05 mmol, 1.10 equiv) was dissolved in anhyd CH_2Cl_2 (30 mL), and oxalyl chloride (387 mg, 0.26 mL, 3.05 mmol, 1.10 equiv) and a catalytic amount of DMF (5 drops) was added. The mixture was stirred at rt for 3 h. Meanwhile thioxanthone **9** (757 mg, 2.77 mmol, 1.00 equiv) was dissolved in anhyd CH_2Cl_2 (65 mL) and cooled to 0 °C. At this temperature, NEt_3 (854 mg, 1.17 mL, 8.31 mmol, 3.00 equiv) and a catalytic amount of 4-dimethylaminopyridine (5 crystals) was added. At 0 °C the freshly prepared solution of acid chloride was added slowly. After addition, the mixture was slowly warmed to rt and stirred overnight. After 18 h, the reaction was stopped with aq NH_4Cl (100 mL) and extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were washed with aq 2 M NaOH (150 mL), dried (Na_2SO_4), and filtered. The solvent was evaporated under reduced pressure and the product was obtained as a yellow solid (1.48 g, 2.74 mmol, 99%); mp 202–206 °C; R_f = 0.83 (CH_2Cl_2/MeOH 98:2) [UV, $KMnO_4$]; $[\alpha]_D^{20}$ –92 (*c* = 1.00, CH_2Cl_2).

IR (ATR): 3089 (w, CH_{sp2}), 2956 (w, CH_{sp3}), 2880 (w, CH_{sp3}), 1759 (s, C=O), 1702 (s, C=O), 1640 (s, C=C_{sp2}), 1338 (s, N=O), 1105 (s, C–O), 730 cm^{-1} (m, C–S).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.45 (d, ^3J = 2.3 Hz, 1 H, H-6$_{ax}$), 1.47 (d, ^3J = 2.3 Hz, 1 H, H-5$_{ax}$), 1.52–1.55 (m, 1 H, H-7), 1.71–1.86 (m, 2 H, H-5$_{eq}$, H-6$_{eq}$), 2.72 (virt. dt, ^2J = 10.9 Hz, $^3J \cong {}^3J$ = 2.0 Hz, 1 H, H-7), 2.94 (s, 1 H, H-1*), 3.01 (s, 1 H, H-4*), 3.31 (dd, ^3J = 9.1 Hz, ^4J = 1.6 Hz, 1 H, H-2), 4.53 (dd, ^3J = 9.1 Hz, ^4J = 1.5 Hz, 1 H, H-3), 7.05 (s, 1 H, H-4′), 7.50–7.57 (m, 2 H, H-5′, H-7′), 7.64–7.74 (m, 3 H, H-6′, H-5″, H-6″), 7.84 (dd, ^3J = 5.4 Hz, ^4J = 3.0 Hz, 2 H, H-4″, H-7″), 8.55 (dd, ^3J = 8.0 Hz, ^4J = 1.5 Hz, 1 H, H-8′), 9.19 (s, 1 H, H-1′).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 28.4 (t, C-6), 29.6 (t, C-5), 37.9 (t, C-7), 40.1 (d, C-1*), 40.5 (d, C-4*), 53.6 (d, C-2), 58.0 (d, C-3), 122.0 (d, C-4′), 123.4 (d, 2 C, C-4″, C-7″), 126.2 (d, C-5′), 127.0 (s, C-9a′), 127.8 (d, C-7′), 128.3 (d, C-1′), 128.5 (s, C-8a′), 130.3 (d, C-8′), 132.0 (s, 2 C, C-3a″, C-7a″), 133.4 (d, C-6′), 134.3 (d, 2 C, C-5″, C-6″), 135.7 (s, C-4b′), 140.1 (s, C-3′), 144.1 (s, C-4a′), 146.0 (s, C-2′), 168.7 (s, 2 C, C-1″, C-3″), 169.0 (s, COO), 177.9 (s, C-9′).

MS (EI, 70 eV): *m*/*z* (%) = 268 (24), 239 (100), 211 (65), 200 (40), 186 (25), 148 (28), 92 (26), 57 (23).

HRMS (EI): *m*/*z* [M]$^+$ calcd for $C_{29}H_{20}N_2O_7S$: 540.0986; found: 540.0993.

(1*R*,2*S*,3*R*,4*S*)-3-(1″,3″-Dioxoisoindolin-2″-yl)-*N*-(3′-hydroxy-9′-oxo-9′*H*-thioxanthen-2′-yl)bicyclo[2.2.1]heptane-2-carboxamide (18)

The ester **17** (400 mg, 741 µmol, 1.00 equiv) was dissolved in THF (26 mL) and H_2O (26 mL) was added. In (425 mg, 3.70 mmol, 5.00 equiv) and concd HCl (0.72 mL) were added. The mixture was heated to 80 °C and stirred for 20 h. After cooling to rt, CH_2Cl_2 (100 mL) was added and the mixture was filtered over Celite. The mixture was washed with aq $NaHCO_3$ (150 mL) and extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were dried

(Na_2SO_4), filtered, and evaporated. The crude material was purified by flash column chromatography (4 × 20 cm, CH_2Cl_2/MeOH 95:5) and the product was isolated as an orange solid (328 mg, 642 µmol, 87%); mp 166–169 °C; R_f = 0.44 (CH_2Cl_2/MeOH 95:5) [UV, $KMnO_4$]; $[\alpha]_D^{20}$ –144 (*c* = 1.00, CH_2Cl_2).

IR (ATR): 3248 (m, OH), 3141 (m, NH), 2967 (w, CH_{sp3}), 2872 (w, CH_{sp3}), 1697 (s, C=O), 1583 (s, $C{=}C_{sp2}$), 1304 (s, C–N), 718 cm^{-1} (s, C–S).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.18–1.38 (m, 2 H, H-5$_{ax}$, H-6$_{ax}$), 1.54–1.60 (m, 1 H, H-7), 1.65–1.80 (m, 2 H, H-5$_{eq}$, H-6$_{eq}$), 2.68 (s, 1 H, H-1), 2.85 (d, ^2J = 11.1 Hz, 1 H, H-7), 3.08–3.15 (m, 2 H, H-2, H-4), 4.44 (dd, ^3J = 8.6 Hz, ^4J = 1.6 Hz, 1 H, H-3), 6.94 (s, 1 H, H-4′), 7.44–7.55 (m, 2 H, H-5′, H-7′), 7.55–7.62 (m, 3 H, H-6′, H-5″, H-6″), 7.76 (dd, ^3J = 5.4 Hz, ^4J = 3.1 Hz, 2 H, H-4″, H-7″), 8.26 (s, 1 H, H-1′), 8.47 (s, 1 H, OH), 8.65 (dd, ^3J = 8.2 Hz, ^4J = 1.5 Hz, 1 H, H-8′), 10.11 (s, 1 H, NH).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 28.8 (t, C-5), 29.3 (t, C-6), 38.4 (t, C-7), 38.7 (d, C-4), 40.9 (d, C-1), 56.0 (d, C-2), 60.0 (d, C-3), 115.2 (d, C-4′), 122.2 (s, C-4a′), 123.5 (d, 2 C, C-4″, C-7″), 123.9 (d, C-1′), 126.3 (d, C-7′), 126.3 (d, C-5′), 127.3 (s, C-3′), 128.8 (s, C-8a′), 129.9 (d, C-8′), 131.6 (s, 2 C, C-3a″, C-7a″), 132.2 (d, C-6′), 134.2 (d, 2 C, C-5″, C-6″), 136.7 (s, C-9a′), 137.4 (s, C-4b′), 153.9 (s, C-2′), 169.6 (s, 2 C, C-1″, C-3″), 173.3 (s, CON), 179.0 (s, C-9′).

MS (EI, 70 eV): *m*/*z* (%) = 205 (25), 91 (28, $[C_6H_3O]^+$), 72 (45), 71 (49, $[C_3H_2NO]^+$), 42 (100).

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{29}H_{22}N_2O_5S$: 510.1249; found: 510.1244.

2-{(1*S*,2*R*,3*S*,4*R*)-3-(10′-Oxo-10′*H*-thioxantheno[2′,3′-*d*]oxazol-2´-yl)bicyclo[2.2.1]heptan-2-yl}isoindoline-1″,3″-dione (19)

The amide **18** (523 mg, 1.03 mmol, 1.00 equiv) was dissolved in anhyd THF (73 mL), and PPh_3 (323 mg, 1.23 mmol, 1.20 equiv) and diisopropyl azodicarboxylate (249 mg, 0.24 mL, 1.23 mmol, 1.20 equiv) were added. The mixture was stirred at rt. After 4 h, the solvent was evaporated and the crude material was purified by flash column chromatography (4 × 25 cm, CH_2Cl_2/MeOH 98:2). The product was isolated as a yellow solid (444 mg, 902 µmol, 88%); mp 223–226 °C; R_f = 0.47 (CH_2Cl_2/MeOH 98:2) [UV, $KMnO_4$]; $[\alpha]_D^{20}$ +30 (*c* = 1.00, CH_2Cl_2).

IR (ATR): 3059 (w, CH_{sp2}), 2991 (w, CH_{sp3}), 2948 (w, CH_{sp3}), 2876 (w, CH_{sp3}), 1766 (m), 1707 (s, CO), 1618 (s, C=N), 1590 (m, $C{=}C_{sp2}$), 1435 (s), 1293 (s), 1100 (m), 743 (m), 714 cm^{-1} (s, C–S).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.51 (d, ^3J = 2.3 Hz, 1 H, H-5), 1.52–1.54 (m, 1 H, H-6), 1.61 (virt. dt, ^2J = 10.7 Hz, $^3J \cong {}^3J$ = 1.6 Hz, 1 H, H-7), 1.77–1.90 (m, 2 H, H-5$_{eq}$, H-6$_{eq}$), 2.87 (virt. dt, ^2J = 10.7 Hz, $^3J \cong {}^3J$ = 2.0 Hz, 1 H, H-7), 2.96 (d, ^3J = 3.6 Hz, 1 H, H-4), 3.01 (d, ^3J = 2.4 Hz, 1 H, H-1), 3.61 (dd, ^3J = 8.8 Hz, ^4J = 1.5 Hz, 1 H, H-3), 4.61 (dd, ^3J = 8.8 Hz, ^4J = 1.5 Hz, 1 H, H-2), 7.39 (s, 1 H, H-4′), 7.43 (dd, ^3J = 8.2 Hz, 7.0 Hz, ^4J = 1.3 Hz, 1 H, H-8′), 7.50 (dd, ^3J = 8.1 Hz, ^4J = 1.5 Hz, 1 H, H-6′), 7.54–7.61 (m, 3 H, H-7′, H-5″, H-6″), 7.63–7.67 (m, 2 H, H-4″, H-7″), 8.51–8.56 (m, 1 H, H-9′), 8.59 (s, 1 H, H-11′).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 28.5 (t, C-5), 30.0 (t, C-6), 38.0 (t, C-7), 39.8 (d, C-4), 41.3 (d, C-1), 49.1 (d, C-3), 58.8 (d, C-2), 106.3 (d, C-4′), 121.8 (d, C-11′), 123.1 (d, 2 C, C-4″, C-7″), 125.6 (d, C-6′), 126.4 (d, C-8′), 126.4 (s, C-4a′), 128.7 (s, C-9a′), 130.0 (s, C-9′), 131.8 (s, 2 C, C-3a″, C-7a″), 132.3 (d, C-7′), 134.0 (d, 2 C, C-5″, C-6″), 137.0 (s, C-5a′), 137.3 (s, C-10a′), 141.1 (s, C-3a′), 152.6 (s, C-11a′), 167.2 (s, 2 C, C-1″, C-3″), 168.6 (s, C-2′), 179.8 (s, C-10′).

MS (EI, 70 eV): *m*/*z* (%) = 492 (1, $[M]^+$), 345 (36, $[C_{21}H_{15}NO_2S]^+$), 317 (100, $[C_{19}H_{11}NO_2S]^+$), 289 (8), 260 (5), 219 (5), 170 (6).

HR-MS (EI): *m*/*z* $[M]^+$ calcd for $C_{29}H_{20}NO_4S$: 492.1144; found: 492.1143.

1-[3″,5″-Bis(trifluoromethyl)phenyl]-3-{(1*S*,2*R*,3*S*,4*R*)-3-(10′-oxo-10′*H*-thioxantheno[2′,3′-d]oxazol-2′-yl)bicyclo[2.2.1]heptan-2-yl}thiourea (2)

The oxazole **19** (70.0 mg, 142 µmol, 1.00 equiv) was suspended in anhyd EtOH (4.5 mL), and anhyd CH_2Cl_2 (4.5 mL) was added. To the solution ethylenediamine (85.0 mg, 0.10 mL, 1.42 mmol, 10.0 equiv) was added. The mixture was warmed to 50 °C and stirred for 20 h. After cooling, the solvent was evaporated and the crude material was filtered by short flash column chromatography (1 × 2 cm, CH_2Cl_2/MeOH 95:5). The isolated product was used in the next step without further purification. The readily prepared amine was dissolved in anhyd THF (8 mL) and isothiocyanate **13** (80.8 mg, 54.0 µL, 298 µmol, 2.10 equiv) was added. The mixture was stirred at rt. After 18 h, the solvent was evaporated and the crude material was purified by flash column chromatography (1 × 5 cm, CH_2Cl_2/MeOH 99:1). The product was isolated as a yellow solid (35.1 mg, 55.4 µmol, 39% over 2 steps); mp 202–204 °C; R_f = 0.21 (CH_2Cl_2/MeOH 99:1) [UV, $KMnO_4$]; $[\alpha]_D^{20}$ –40 (*c* = 1.00, CH_2Cl_2).

IR (ATR): 3281 (m, NH), 3063 (w, CH_{sp2}), 2960 (w, CH_{sp3}), 2925 (w, CH_{sp3}), 2876 (w, CH_{sp3}), 1766 (w), 1719 (s, C=O), 1637 (m), 1618 (s, C=N), 1591 (m), 1435 (s), 1370 (m), 1275 (s, C=S), 1173 (m), 1132 (s), 1110 (m), 715 cm^{-1} (m, C–S).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.60–1.79 (m, 5 H, H-5, H-6, H-7), 1.94 (d, ^2J = 11.4 Hz, 1 H, H-7), 2.58 (s, 1 H, H-4), 3.13 (s, 1 H, H-1), 3.37 (s, 1 H, H-3), 4.32 (s, 1 H, H-2), 6.67 (s, 1 H, NH), 7.52 (ddd, ^3J = 8.2 Hz, 7.0 Hz, ^4J = 1.3 Hz, 1 H, H-8′), 7.58 (dd, ^3J = 7.8 Hz, ^4J = 1.3 Hz, 1 H, H-6′), 7.62–7.68 (m, 1 H, H-7′), 7.67 (s, 1 H, H-4′), 7.76 (s, 1 H, H-4″), 8.23 (s, 2 H, H-2″), 8.67 (dd, ^3J = 8.2 Hz, ^4J = 1.4 Hz, 1 H, H-9′), 8.92 (s, 1 H, H-11′), 10.40 (s, 1 H, NH).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 28.8 (t, C-5), 29.5 (t, C-6), 29.9 (t, C-7), 37.5 (d, C-4), 43.6 (d, C-1), 61.3 (d, C-3), 63.3 (d, C-2), 107.4 (d, C-4″), 116.5 (d, C-4′), 118.9 (s, C-1″), 121.4 (d, C-11′), 124.0 (d, 2 C, C-2″), 124.3 (s, 2 C, C-3″), 125.8 (d, C-8′), 126.6 (q, $^1J_{CF}$ = 211 Hz, 2 C, CF_3), 126.8 (d, C-7′*), 127.4 (s, C-4a′), 128.8 (d, C-9′), 130.4 (s, C-9a′), 132.7 (d, C-6′*), 136.7 (s, C-5a′), 139.0 (s, C-10a′), 141.0 (s, C-3a′), 153.4 (s, C-11a′), 170.3 (s, C-2′), 182.9 (s, C-10′), 186.6 (s, NCSN).

MS (EI, 70 eV): *m*/*z* (%) = 633 (1, $[M]^+$), 362 (12), 345 (39, $[C_{21}H_{15}NO_2S]^+$), 317 (52, $[C_{19}H_{11}NO_2S]^+$), 271 (100, $[C_9H_4F_6NS]^+$), 229 (18), 213 (24), 163 (13).

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{30}H_{22}F_6N_3O_2S_2$: 634.1052; found: 634.1047.

(1*R*,2*S*)-2-Aminocyclohexane-1-carboxylic Acid Hydrochloride (21)

Amino acid **20** (3.00 g, 12.1 mmol, 1.00 equiv) was dissolved in aq 6 N HCl (150 mL). The mixture was stirred at 120 °C for 48 h. After this time, the solvent was evaporated and the product was obtained as a colorless solid (2.15 g, 12.0 mmol, 99%); mp 198–220 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.11–2.06 (m, 8 H, H-3, H-4, H-5, H-6), 2.89 (virt. q, $^3J \cong {}^3J$ = 4.4 Hz, 1 H, H-1), 3.08–3.41 (m, 1 H, H-2), 8.06 (s, 3 H, NH_3), 12.90 (s, 1 H, COOH).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 22.0 (t, C-4), 22.2 (t, C-5), 25.5 (t, C-6), 27.0 (t, C-3), 41.8 (d, C-1), 48.8 (d, C-2), 174.0 (s, COOH).

The analytical data are in accordance with the literature.[27]

(1*R*,2*S*)-2-(1′,3′-Dioxoisoindolin-2′-yl)cyclohexane-1-carboxylic Acid (22)

Hydrochloride **21** (493 mg, 2.75 mmol, 1.00 equiv) was dissolved in anhyd toluene (50 mL). Subsequently phthalic anhydride (427 mg, 2.88 mmol, 1.05 equiv) and NEt_3 (556 mg, 0.76 mL, 5.49 mmol, 2.00 equiv) were added. The mixture was stirred at 100 °C. After 18 h, the solution was cooled and washed with aq 3 M HCl (150 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 150 mL). The combined organic layers were dried (Na_2SO_4) and filtered. The solvent was removed under reduced pressure. The desired product was obtained as a colorless solid (743 mg, 2.72 mmol, 99%); mp 144–146 °C; $[\alpha]_D^{20}$ –52 (*c* = 1.00, CH_2Cl_2).

IR (ATR): 3285 (m, OH), 2960 (m, CH_{sp3}), 2925 (w, CH_{sp3}), 2868 (m, CH_{sp3}), 1719 (s, C=O), 1690 (s, C=O), 1405 (m), 1372 (s, C–N), 1331 (m), 1184 (m), 1082 (m), 1018 (m), 713 cm^{-1} (m, CH_{sp2}).

^1H NMR (400 MHz, $CDCl_3$): δ = 1.33–1.44 (m, 1 H, H-5), 1.55 (virt. dt, ^3J = 13.8 Hz, $^3J \cong {}^3J$ = 4.0 Hz, 1 H, H-6), 1.66 (virt. ddt, ^3J = 13.8 Hz, 12.4 Hz, $^3J \cong {}^3J$ = 4.6 Hz, 1 H, H-5), 1.77 (dd, ^3J = 13.2 Hz. 3.6 Hz, 1 H, H-4), 1.90–2.01 (m, 2 H, H-6, H-3), 2.15 (virt. dt, ^3J = 13.8 Hz, $^3J \cong {}^3J$ = 2.8 Hz, 1 H, H-4), 2.82 (virt. dq, ^3J = 12.7 Hz, $^3J \cong {}^3J$ = 3.4 Hz, 1 H, H-3), 3.00 (virt. q, $^3J \cong {}^3J$ = 2.9 Hz, 1 H, H-1), 4.33 (ddd, ^3J = 12.7 Hz, 5.3 Hz, 3.5 Hz, 1 H, H-2), 7.66 (dd, ^3J = 5.5 Hz, ^4J = 3.0 Hz, 2 H, H-5′, H-6′), 7.77 (dd, ^3J = 5.5 Hz, ^4J = 3.0 Hz, 2 H, H-4′, H-7′), 8.42 (br s, 1 H, COOH).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 21.6 (t, C-5), 26.0 (t, C-6), 26.1 (t, C-4), 27.5 (t, C-3), 42.9 (d, C-1), 52.8 (d, C-2), 123.8 (d, 2 C, C-4′, C-7′), 132.0 (s, 2 C, C-3a′, C-7a′), 134.0 (d, 2 C, C-5′, C-6′), 168.7 (s, 2 C, C-1′, C-3′), 178.0 (s, COOH).

MS (EI, 70 eV): *m*/*z* (%) = 273 (12, $[M]^+$), 256 (25, $[C_{15}H_{13}NO_3]^+$), 227 (15), 186 (23), 148 (33, $[C_8H_6NO_2]^+$), 91 (100).

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{15}H_{15}NO_4$: 273.1001; found: 273.0996.

2′-Nitro-9′-oxo-9′*H*-thioxanthen-3′-yl (1*R*,2*S*)-2-(1″,3″-Dioxoisoindolin-2˝-yl)cyclohexane-1-carboxylate (23)

The protected amino acid **22** (450 mg, 1.65 mmol, 1.10 equiv) was dissolved in anhyd CH_2Cl_2 (20 mL) and oxalyl chloride (209 mg, 0.14 mL, 1.65 mmol, 1.10 equiv) and a catalytic amount of DMF (5 drops) was added at rt. The mixture was stirred at rt for 3 h. Meanwhile thioxanthone **9** (388 mg, 1.50 mmol, 1.00 equiv) and a catalytic amount of 4-dimethylaminopyridine (5 crystals) was dissolved in anhyd CH_2Cl_2 (45 mL) and cooled to 0 °C. At this temperature, NEt_3 (456 mg, 0.63 mL, 4.50 mmol, 3.00 equiv) was added. At 0 °C the readily prepared solution of acid chloride was added slowly. The mixture was warmed to rt and stirred overnight. After 18 h, aq NH_4Cl (80 mL) was added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 100 mL) and the combined organic layers were washed with aq 2 M NaOH (150 mL), dried (Na_2SO_4), and filtered. The solvent was evaporated and the desired product was obtained without further purification as a yellowish solid (768 mg, 1.46 mmol, 97%); mp 188–190 °C; R_f = 0.86 (CH_2Cl_2/MeOH 98:2) [UV, $KMnO_4$]; $[\alpha]_D^{20}$ –216 (*c* = 1.00, CH_2Cl_2).

IR (ATR): 2948 (w, CH_{sp3}), 2887 (w, CH_{sp3}), 2847 (w, CH_{sp3}), 1779 (s, C=O), 1709 (s, C=O), 1644 (s, C=O), 1592 (s, CH_{sp2}), 1522 (s, NO_2), 1340 (s, NO_2), 1077 (s), 1049 (s), 1017 (s), 743 (s, CH_{sp2}), 723 (s, CH_{sp2}), 693 cm^{-1} (C–S–C).

^1H NMR (400 MHz, $CDCl_3$): δ = 1.50 (virt. dt, $^3J \cong {}^3J$ = 13.3 Hz, 3.9 Hz, 1 H, H-5), 1.66–1.70 (m, 1 H, H-4), 1.79–1.89 (m, 2 H, H-3, H-6), 1.97–2.06 (m, 2 H, H-4, H-5), 2.40 (d, ^3J = 14.7 Hz, 1 H, H-6), 2.91 (virt. dq, ^3J = 12.8 Hz. $^3J \cong J$ = 3.2 Hz, 1 H, H-3), 3.38 (virt. q, $^3J \cong {}^3J$ = 4.2 Hz, 1 H, H-1), 4.48 (ddd, ^3J = 12.8 Hz, 5.1 Hz, 3.5 Hz, 1 H, H-2), 7.57 (ddd, ^3J = 8.2 Hz. 7.1 Hz, ^4J = 1.2 Hz, 1 H, H-7′), 7.60–7.63 (m, 2 H, H-4′, H-5′), 7.69–7.74 (m, 3 H, H-6′, H-5″, H-6″), 7.86 (dd, ^3J = 5.4 Hz, ^4J = 3.0 Hz, 2 H, H-4″, H-7″), 8.60 (dd, ^3J = 8.2 Hz, ^4J = 1.5 Hz, 1 H, H-8′), 9.24 (s, 1 H, H-1′).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 21.0 (t, C-4), 26.0 (t, C-5), 26.2 (t, C-3), 27.9 (t, C-6), 44.0 (d, C-1), 52.7 (d, C-2), 122.7 (d, C-4′), 123.4 (d, 2 C, C-4″, C-7″), 126.3 (d, C-5′), 127.0 (s, C-9′), 127.7 (d, C-7′), 128.3 (d, C-1′), 128.6 (s, C-8a′), 130.3 (d, C-8′), 132.0 (s, 2 C, C-3a″, C-7a″), 133.4 (d, C-6′), 134.4, (d, 2 C, C-5″, C-6″) 136.0 (s, C-4b′), 140.2 (s, C-3′), 144.2 (s, C-4a′), 146.2 (s, C-2′), 168.8 (s, 2 C, C-1″, C-3″), 170.3 (s, COO), 178.0 (s, C-9′).

MS (EI, 70 eV): *m*/*z* (%) = 528 (1, $[M]^+$), 273 (32, $[C_{13}H_7NO_4S]^+$), 256 (100, $[C_{15}H_{14}NO_3]^+$), 148 (75, $[C_8H_6NO_2]^+$).

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{28}H_{20}N_2O_7S$: 528.0991; found: 528.0992.

(1*R*,2*S*)-2-(1′,3′-Dioxoisoindolin-2′-yl)-*N*-(3″-hydroxy-9″-oxo-9″*H*-thioxanthen-2″-yl)cyclohexane-1-carboxamide (24)

Ester **23** (699 mg, 1.36 mmol, 1.00 equiv) was dissolved in THF (40 mL) and H_2O (40 mL) was added. To this solution In (780 mg, 6.80 mmol, 5.00 equiv) and concd HCl (1.12 mL) were added. The mixture was stirred at 80 °C and after 18 h, the solution was cooled to rt and CH_2Cl_2 (50 mL) was added. The mixture was filtered over Celite and washed with aq $NaHCO_3$ (100 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 150 mL). The combined organic layers were dried (Na_2SO_4), filtered, and the solvent was removed under reduced pressure. Purification by flash chromatography (4 × 20 cm, CH_2Cl_2/MeOH 95:5) afforded the title product as an orange solid (597 mg, 1.24 mmol, 91%); mp 136–138 °C; R_f = 0.59 (CH_2Cl_2/MeOH 95:5) [UV, $KMnO_4$]; $[\alpha]_D^{20}$ –4 (*c* = 1.00, CH_2Cl_2).

IR (ATR): 3262 (w, OH), 2933 (w, CH_{sp3}), 2851 (w, CH_{sp3}), 2552 (w, CONH), 1769 (m, C=O), 1708 (s, C=O), 1658 (m, CONH), 1607 (s, CH_{sp2}), 1589 (s, CH_{sp2}), 1523 (s, CONH), 1490 (s), 1437 (s), 1077 (s), 1016 (s), 742 (CH_{sp2}), 707 cm^{-1} (s, CH_{sp2}).

^1H NMR (400 MHz, $CDCl_3$): δ = 1.38–1.49 (m, 1 H, H-4), 1.57–1.62 (m, 1 H, H-5), 1.70 (virt. dt, ^3J = 13.3 Hz, $^3J \cong {}^3J \cong$ 4.2 Hz, 1 H, H-3), 1.78 (virt. dt, ^3J = 13.1 Hz, $^3J \cong {}^3J \cong$ 4.6 Hz, 1 H, H-6), 1.99–2.08 (m, 1 H, H-4), 2.08–2.22 (m, 1 H, H-5), 2.24–2.31 (m, 1 H, H-6), 2.97 (virt. dq ^3J = 12.4 Hz, $^3J \cong {}^3J$ = 3.7 Hz, 1 H, H-3), 3.17 (virt. q, $^3J \cong {}^3J$ = 4.5 Hz, 1 H, H-1), 4.35 (ddd, ^3J = 12.4 Hz, 5.1 Hz, 3.8 Hz, 1 H, H-2), 7.15 (s, 1 H, H-4′), 7.48 (ddd, ^3J = 8.2 Hz, 6.7 Hz, ^4J = 1.5 Hz, 1 H, H-7′), 7.52–7.65 (m, 5 H, H-4″, H-5″, H-6″, H-7″, H-5′), 7.62 (ddd, ^3J = 8.2 Hz, 6.7 Hz, ^4J = 1.5 Hz, 1 H, H-6′), 7.88 (s, 1 H, H-1′), 8.42 (dd, ^3J = 8.2 Hz, ^4J = 1.5 Hz, 1 H, H-8′), 9.14 (s, 1 H, OH), 10.65 (s, 1 H, NH).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 21.2 (t, C-5), 25.8 (t, C-4), 25.9 (t, C-3), 28.9 (t, C-6), 45.0 (d, C-1), 52.6 (d, C-2), 115.4 (d, C-4′), 122.0 (s, C-4a′), 123.4 (d, 2 C, C-4″, C-7″), 124.1 (d, C-1′), 126.2 (d, C-7′), 126.3 (d, C-5′), 127.0 (s, C-3′), 128.7 (s, C-8a′), 129.4 (d, C-8′), 131.4 (s, 2 C, C-3a″, C-7a″), 132.3 (d, C-6′), 134.2 (d, 2 C, C-5″, C-6″), 137.0 (s, C-9a′), 137.7 (s, C-4b′), 154.7 (s, C-2′), 168.6 (s, 2 C, C-1″, C-3″), 175.3 (s, CONH), 179.5 (s, C-9′).

MS (EI, 70 eV): *m*/*z* (%) = 498 (5, $[M]^+$), 256 (30, $[C_{15}H_{14}NO_3]^+$), 227 (38, $[C_{14}H_{13}NO_2]^+$), 148 (43, $[C_8H_4NO_2]^+$), 111 (55).

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{28}H_{22}N_2O_5S$: 499.1322; found: 499.1322.

2-{(1*S*,2*R*)-2-(10′-Oxo-10′*H*-thioxantheno[2′,3′-*d*]oxazol-2′-yl)cyclohexyl}isoindoline-1″,3″-dione (25)

The synthesized amide **24** (575 mg, 1.15 mmol, 1.00 equiv) was dissolved in anhyd THF (55 mL). At rt, PPh_3 (666 mg, 2.54 mmol, 2.20 equiv) and diisopropyl azodicarboxylate (513 mg, 0.50 mL, 2.54 mmol, 2.20 equiv) were added. The mixture was stirred at rt for 4 h. After this time, the solvent was evaporated. The crude product was purified by flash chromatography (4 × 25 cm, CH_2Cl_2/MeOH 98:2). The desired product was obtained as a yellow solid (510 mg, 1.06 mmol, 89%); mp 95–98 °C; R_f = 0.64 (CH_2Cl_2/MeOH 98:2) [UV, $KMnO_4$]; $[\alpha]_D^{20}$ –176 (*c* = 1.00, CH_2Cl_2).

IR (ATR): 2932 (w, CH_{sp3}), 2357 (w), 1708 (s, C=O), 1637 (m, C=N), 1619 (s, $C{=}C_{sp2}$), 1436 (s, CH_{sp3}), 1366 (s, CH_{sp3}), 1292 (s), 1108 (m), 740 (s, CH_{sp2}), 716 (s, CH_{sp2}), 698 cm^{-1} (m, C–S–C).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.56 (virt. ddt, ^3J = 13.6 Hz, 9.6 Hz, $^3J \cong {}^3J$ = 4.7 Hz, 1 H, H-5), 1.71–1.80 (m, 2 H, H-4, H-6), 1.98–2.06 (m, 1 H, H-3), 2.13–2.16 (m, 1 H, H-5), 2.30–2.34 (m, 1 H, H-3), 2.37 (virt. dt, ^3J = 13.4 Hz, $^3J \cong {}^3J$ = 4.1 Hz, 1 H, H-4), 2.88 (virt. dq, ^3J = 13.2 Hz, $^3J \cong {}^3J$ = 3.6 Hz, 1 H, H-6), 3.69–3.71 (m, 1 H, H-2), 4.59 (ddd, ^3J = 13.2 Hz, 5.3 Hz, 3.6 Hz, 1 H, H-1), 7.49 (ddd, ^3J = 8.1 Hz, 6.9 Hz, ^4J = 1.4 Hz, 1 H, H-8′), 7.57 (dd, ^3J = 8.2 Hz, ^4J = 1.3 Hz, 1 H, H-6′), 7.60 (s, 1 H, H-4′), 7.63 (ddd, ^3J = 8.2 Hz, 6.9 Hz, ^4J = 1.4 Hz, 1 H, H-7′), 7.67–7.73 (m, 4 H, H-4″, H-5″, H-6″, H-7″), 8.63 (dd, ^3J = 8.1 Hz, ^4J = 1.4 Hz, 1 H, H-9′), 8.89 (s, 1 H, H-11′).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 21.3 (t, C-5), 25.6 (t, C-6), 26.4 (t, C-4), 28.5 (t, C-3), 39.1 (d, C-2), 53.2 (d, C-1), 106.6 (d, C-4′), 122.0 (d, C-11′), 123.4 (d, 2 C, C-4″, C-7″), 125.7 (d, C-6′), 126.4 (d, C-8′), 126.7 (s, C-4a′), 128.9 (s, C-9a′), 130.1 (d, C-9′), 131.9 (s, 2 C, C-3a″, C-7a″), 132.4 (d, C-7′), 134.2 (d, 2 C, C-5″, C-6″), 137.2 (s, C-5a′), 137.8 (s, C-10a′), 141.1 (s, C-3a′), 153.4 (s, C-11a′), 168.4 (s, 2 C, C-1″, C-3″), 168.6 (s, C-2′), 180.0 (s, C-10′).

MS (EI, 70 eV): *m*/*z* (%) = 480 (3, $[M]^+$), 333 (100, $[C_{20}H_{15}NO_3S]^+$).

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{28}H_{20}N_2O_4S$: 481.1217; found: 481.1217.

1-[3″,5″-Bis(trifluoromethyl)phenyl]-3-{(1*S*,2*R*)-2-(10′-oxo-10′*H*-thioxantheno[2′,3′-*d*]oxazol-2′-yl)cyclohexyl}thiourea (3)

To a solution of oxazole **25** (510 mg, 1.06 mmol, 1.00 equiv) in anhyd EtOH (35 mL) were added anhyd CH_2Cl_2 (35 mL) and ethylenediamine (638 mg, 0.71 mL, 10.6 mmol, 10.0 equiv) and the mixture was stirred at 50 °C for 24 h. After this time, the solvent was evaporated, diluted with CH_2Cl_2, and filtered over SiO_2. After evaporation of the solvent, the crude material was used in the next step without further purification. The crude material was dissolved in anhyd THF (70 mL) and 1-isothioxyanato-3,5-bis(trifluoromethyl)benzene (575 mg, 0.39 mL, 2.12 mmol, 2.00 equiv) was added. The reaction mixture was stirred at rt and after 18 h, the solvent was evaporated. Purification by flash chromatography (2 × 15 cm, Pn/EtOAc 4:1) afforded the final thiourea as a yellow solid (300 mg, 0.48 mmol, 46% over 2 steps); mp 126–128 °C; R_f = 0.22 (Pn/EtOAc 4:1) [UV, $KMnO_4$]; $[\alpha]_D^{20}$ –216 (*c* = 1.00, CH_2Cl_2).

IR (ATR): 2936 (w, CH_{sp3}), 1711 (s, C=O), 1607 (m, $C{=}C_{sp2}$), 1589 (m, $C{=}C_{sp2}$), 1520 (s, $C{=}C_{sp2}$), 1436 (s, CH_{p3}), 1383 (s), 1274 (s), 1174 (s), 1129 (s), 743 (s, CH_{p3}), 698 cm^{-1} (m, C–S–C).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.51–1.89 (m , 6 H, H-3, H-4, H-5, H-6), 1.99–2.15 (m, 2 H, H-3, H-6), 3.79 (virt. td, $^3J \cong {}^3J$ = 7.4 Hz, ^3J = 4.3 Hz, 1 H, H-2), 4.99 (virt. tt, $^3J \cong {}^3J$ = 8.3 Hz, 4.0 Hz, 1 H, H-1), 7.58 (ddd, ^3J = 8.2, 6.8 Hz, ^4J = 1.5 Hz, 1 H, H-8′), 7.62 (s, 1 H, H-4′), 7.70–7.84 (m, 2 H, H-6′, H-7′), 8.07 (d, ^3J = 8.6 Hz, 1 H, NH), 8.16 (s, 1 H, H-4″), 8.20 (s, 2 H, H-2″), 8.49 (dd, ^3J = 8.2 Hz, ^4J = 1.4 Hz, 1 H, H-9′), 8.73 (s, 1 H, H-11′), 9.97 (s, 1 H, NH).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 22.1 (t, C-4*), 22.4 (t, C-5*), 25.9 (t, C-3), 28.3 (t, C-6), 38.8 (d, C-2), 52.0 (d, C-1), 107.7 (d, C-4″), 116.1 (d, C-4′), 116.2 (s, C-1″), 120.0 (d, C-11′) 120.9 (q, $^1J_{C,F}$ = 183 Hz, 2 C, CF_3), 121.8 (d, 2 C, C-2″), 126.1 (q, $^2J_{C,F}$ = 109 Hz, 2 C, C-3″), 126.2 (d, C-7′*), 126.7 (d, C-8′), 127.7 (s, C-4a′), 129.1 (d, C-9′), 132.9 (d, C-6′*), 133.5 (s, C-9a′), 136.5 (s, C-5a′), 140.7 (s, C-10a′), 141.6 (s, C-3a′), 152.6 (s, C-11a′), 169.1 (s, C-2′), 178.6 (s, NCSN), 179.9 (s, C-10′).

MS (EI, 70 eV): *m*/*z* (%) = 621 (1, $[M]^+$), 578 (2, $[C_{29}H_{19}F_6N_3O_2S]^+$), 392 (15, $[C_{16}H_{12}F_6N_3S]^+$), 333 (63, $[C_{10}H_{18}F_3N_3O_2S_2]^+$), 271 (100, $[C_9H_4F_6NS]^+$), 229 (67, $[C_8H_5F_6N]^+$).

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{29}H_{21}F_6N_3O_2S_2$: 622.1052; found: 622.1045.

***tert*-Butyl [(1*S*,2*R*)-2-(Hydroxymethyl)cyclohexyl]carbamate (27)**

To a solution of [(1*S*,2*R*)-2-aminocyclohexyl]methanol (**26**; 130 mg, 1.01 mmol, 1.00 equiv) in CH_2Cl_2 (2 mL) was added Et_3N (280 µL, 203 mg, 2.01 mmol, 2.00 equiv). The solution was cooled to 0 °C and Boc_2O (230 mg, 1.06 mmol, 1.05 equiv) was added. The solution was stirred and allowed to warm to rt overnight. The reaction was quenched by the addition of aq 1 M HCl. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 5 mL). The organic layers were combined and successively washed with aq $NaHCO_3$ (2 × 15 mL) and brine (2 × 15 mL), and dried (Na_2SO_4). The solvent was removed under reduced pressure and the residue was purified by flash chromatography (3 × 10 cm, Chx/EtOAc 9:1 → 4:1). Product **27** was obtained as a yellow oil (213 mg, 928 µmol, 92%); R_f = 0.17 (Chx/EtOAc 4:1) [UV, KMnO4]; $[\alpha]_D^{20}$ –30 (*c* = 1.00, CH_2Cl_2).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.86–0.98 (m, 1 H, H-5), 1.14–1.36 (m, 3 H, H-3, H-4, H-6), 1.45 [s, 9 H, $C(CH_3)_3$], 1.52–1.83 (m, 5 H, H-2, H-3, H-5, H-6, OH), 3.21 (virt. t, $^3J \cong {}^3J$ = 11.4 Hz, 1 H, C*H*HOH), 3.34 (dd, ^2J = 11.9 Hz, ^3J = 4.7 Hz, 1 H, CH*H*OH), 4.04–4.07 (m, 1 H, H-1), 4.77 (d, ^3J = 9.0 Hz, 1 H, NH).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 21.0 (t, C-5), 23.1 (t, C-4), 24.9 (t, C-3), 28.2 (q, CH_3), 30.3 (t, C-6), 43.1 (d, C-2), 45.1 (d, C-1), 63.9 (t, CH_2OH), 80.0 [s, *C*$(CH_3)_3$], 157.2 (s, NHCO).

The spectroscopic data match the literature values.[30a]

***tert*-Butyl [(1*S*,2*R*)-2-Formylcyclohexyl]carbamate (28)**

A solution of oxalyl chloride (0.55 mL, 824 mg, 6.50 mmol, 1.00 equiv) in CH_2Cl_2 (16 mL) was cooled to –78 °C, before a solution of DMSO (1.38 mL, 1.52 g, 19.5 mmol, 3.00 equiv) in CH_2Cl_2 (2 mL) was added dropwise. The solution was stirred for 1 h at –78 °C. Subsequently, a solution of carbamate **27** (1.49 g, 6.50 mmol, 1.00 equiv) in CH_2Cl_2 (7 mL) was added slowly over 10 min. After an additional 10 min, NEt_3 (4.50 mL, 3.30 g, 32.5 mmol, 5.00 equiv) was added. The reaction mixture was stirred for an additional 15 min at –78 °C and then allowed to warm to rt. The reaction was quenched by the addition of H_2O (20 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 20 mL). The combined organic layers were washed successively with aq NH_4Cl (1 × 60 mL) and brine (1 × 60 mL), dried (Na_2SO_4), and filtered. All volatiles were removed under reduced pressure and the product **28** was obtained as a brownish solid (1.39 g, 6.12 mmol, 94%) and used in the next step without further purification; mp 23–25 °C; $[\alpha]_D^{20}$ +82.4 (*c* = 0.17, CH_2Cl_2).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.19–1.38 (m, 1 H, H-5), 1.43 [s, 9 H, $C(CH_3)_3$], 1.53–1.77 (m, 6 H, H-3, H-4, H-5, H-6), 1.91–2.01 (m, 1 H, H-3), 2.71 (virt. q, $^3J \cong {}^3J$ = 4.6 Hz, 1 H, H-2), 3.97 (virt. tt, $^3J \cong$ 9.1, 4.1 Hz, 1 H, H-1), 5.15–5.31 (m, 1 H, NH), 9.70 (d, ^3J = 4.2 Hz, 1 H, CHO).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 22.9 (t, C-3), 23.7 (t, C-5), 23.9 (t, C-4), 28.5 (q, CH_3), 29.8 (t, C-6), 48.2 (d, C-1), 52.1 (d, C-2), 79.6 [s, $C(CH_3)_3$], 155.5 (s, NHCO), 204.8 (s, CHO).

The spectroscopic data match the literature values.[30a]

tert-Butyl [(1*S*,2*S*)-2-Ethynylcyclohexyl]carbamate (29)

A solution of dimethyl(diazomethyl)phosphonate (1.90 g, 12.6 mmol, 2.05 equiv) in THF (15 mL) was cooled to –78 °C. KO^{t}Bu (1.45 g, 12.9 mmol, 2.10 equiv) was added and the solution was stirred for 1 h. Subsequently, a solution of aldehyde **28** (1.39 g, 6.16 mmol, 1.00 equiv) in THF (190 mL) was added slowly. The reaction mixture was stirred for 15 h and was allowed to warm to rt during that time. The reaction was quenched by the addition of aq NH_4Cl (80 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 × 80 mL). The combined organic layers were successively washed with aq NH_4Cl (2 × 250 mL) and brine (2 × 250 mL), dried (Na_2SO_4), and all the volatiles were removed under reduced pressure. The crude product was purified by flash chromatography (4 × 20 cm, Chx/EtOAc 10:1) to afford **29** as a colorless solid (0.91 g, 4.07 mmol, 67%); mp 50 °C; R_f = 0.64 (Chx/EtOAc 4:1) [UV, $KMnO_4$]; $[\alpha]_D^{20}$ –24 (c = 1.00, CH_2Cl_2).

IR (ATR): 3437 (w, N–H), 3309 (w, C–H), 2977 (w, CH_3), 2934 (m, CH_2), 2860 (w, C–H), 2111 (w, C≡C), 1702 (s, C=O), 1497 (s, N–H), 1365 (m), 1245 (m), 1165 (s), 944 (w), 864 (w), 779 (w), 626 cm^{-1} (m).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.22–1.34 (m, 1 H, H-5), 1.44 [s, 9 H, $C(CH_3)_3$], 1.48–1.66 (m, 4 H, H-3, H-4, H-6), 1.67–1.76 (m, 2 H, H-5, H-6), 1.80–1.89 (m, 1 H, H-3), 2.11 (d, ^4J = 2.5 Hz, 1 H, C≡CH), 2.96 (br s, 1 H, H-2), 3.56 (virt. ddt, ^3J = 13.1 Hz, 8.6 Hz, $^3J \cong {}^3J$ = 4.0 Hz, 1 H, H-1), 4.80 (d, ^3J = 9.4 Hz, 1 H, NH).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 20.8 (t, C-4), 25.1 (t, C-5), 28.6 (q, CH_3), 29.0 (t, C-6), 30.2 (t, C-3), 33.4 (d, C-2), 50.5 (d, C-1), 71.9 (d, C≡CH), 79.4 [s, $C(CH_3)_3$], 84.1 (s, C≡CH), 155.2 (s, NHCO).

MS (EI, 70 eV): m/z (%) = 167 (30, $[C_9H_{13}NO_2]^+$), 123 (27, $[C_9H_{13}N]^+$), 106 (27, $[C_8H_{10}]^+$), 57 (100, $[C_4H_8]^+$).

HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{13}H_{22}NO_2$: 224.1645; found: 224.1645.

tert-Butyl {(1*S*,2*S*)-2-[(9′-Oxo-9′*H*-thioxanthen-2′-yl)-ethynyl]cyclohexyl}carbamate (31)

Alkyne **29** (80 mg, 360 µmol, 1.00 equiv) and bromothioxanthone **30**[34] (114 mg, 394 µmol, 1.10 equiv) were dissolved in anhyd THF (18 mL) and freshly distilled NEt_3 (18 mL). The solution was degassed three times by the freeze-pump-thaw[37] method. Subsequently, $Pd(PPh_3)_4$ (41.4 mg, 35.8 µmol, 0.10 equiv) and CuI (13.6 mg, 71.6 µmol, 0.20 equiv) were added and the mixture was again degassed four times by the freeze-pump-thaw method. The mixture was heated to 60 °C for 16 h in a sealed tube. After cooling to rt, the volatiles were removed under reduced pressure. The black residue was dissolved in CH_2Cl_2 (20 mL) and the organic layer was washed successively with aq NH_4Cl (2 × 20 mL) and brine (2 × 20 mL). The organic layer was dried (Na_2SO_4) and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography (2 × 20 cm, Chx/EtOAc 50:1 → 20:1 → 5:1) to give the title compound as a bright yellow solid (121 mg, 280 µmol, 78%); mp 185–187 °C; R_f = 0.16 (Chx/EtOAc 20:1) [UV, $KMnO_4$]; $[\alpha]_D^{20}$ –154 (c = 1.00, CH_2Cl_2).

IR (ATR): 3364 (w, N–H), 3058 (w, ArH), 2973 (w, CH_3), 2934 (w, CH_2), 2859 (w, C–H), 2221 (w, C≡C), 1681 (m, C=O), 1642 (m, C=O), 1438 (m, N–H), 1248 (m), 1162 (m), 894 (w), 825 (w), 743 (m), 620 cm^{-1} (w).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.32–1.40 (m, 1 H, H-5), 1.47 [s, 9 H, $C(CH_3)_3$], 1.57–1.71 (m, 4 H, H-3, H-4, H-6), 1.75–1.81 (m, 2 H, H-5, H-6), 1.93–2.02 (m, 1 H, H-3), 3.18–3.26 (m, 1 H, H-2), 3.62–3.72 (m, 1 H, H-1), 4.85 (d, ^3J = 9.5 Hz, 1 H, NH), 7.53 (dd, ^3J = 7.2 Hz, ^4J = 1.4 Hz, 1 H, H-4′), 7.55 (d, ^3J = 8.4 Hz, 1 H, H-7′), 7.61 (dd, ^3J = 8.1 Hz, ^4J = 1.4 Hz 1 H, H-5′), 7.64–7.66 (m, 2 H, H-3′, H-6′), 8.63 (dd, ^3J = 8.1 Hz, ^4J = 1.5 Hz, 1 H, H-8′), 8.66 (d, ^4J = 1.8 Hz, 1 H, H-1′).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 21.2 (t, C-4), 25.2 (t, C-5), 28.6 (q, CH_3), 29.5 (t, C-6), 30.6 (t, C-3), 34.4 (d, C-2), 51.0 (d, C-1), 79.6 [s, $OC(CH_3)_3$], 83.2 (s, CHC≡CAr), 91.3 (s, CHC≡CAr), 122.0 (s, C-2′), 126.1 (d, C-5′), 126.2 (d, C-4′), 126.7 (d, C-7′), 128.8 (s, C-8a′), 129.2 (s, C-1a′), 130.1 (d, C-8′), 132.6 (d, C-6′), 133.1 (d, C-1′), 135.1 (d, C-3′), 136.8 (s, C-4a′), 137.1 (s, C-5a′), 155.3 (s, NHCO), 179.5 (s, C=O).

MS (EI, 70 eV): m/z (%) = 333 (100, [M – CO_2t-Bu]$^+$), 290 (89, $[C_{19}H_{14}OS]^+$), 237 (92, $[C_{15}H_9OS]^+$), 139 (11, $[C_7H_7OS]^+$).

HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{26}H_{28}NO_3S$: 434.1784; found: 434.1784.

2′-{[(1*S*,2*S*)-2-Aminocyclohexyl]ethynyl}-9′*H*-thioxanthen-9′-one (32)

Boc-protected amine **31** (75 mg, 173 µmol, 1.00 equiv) was dissolved in CH_2Cl_2 (2 mL) and cooled to 0 °C. TFA (132 µL, 197 mg, 1.73 mmol, 10.0 equiv) was slowly added and the solution was stirred at rt for 2 h. The reaction was quenched by the addition of H_2O (5 mL) and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 5 mL). The combined organic layers were successively washed with aq $NaHCO_3$ (2 × 15 mL) and brine (1 × 15 mL), dried (Na_2SO_4), and the volatiles were removed under reduced pressure. The crude product was purified by flash column chromatography (2 × 20 cm, CH_2Cl_2/MeOH 19:1 + 1 vol% NH_3) to give the title compound as a slowly crystallizing yellow oil (43.3 mg, 130 µmol, 78%); R_f = 0.54 (CH_2Cl_2/MeOH 9:1 + 1 vol% NH_3) [UV, $KMnO_4$]; $[\alpha]_D^{20}$ –66 (c = 1.00, CH_2Cl_2).

IR (ATR): 3360 (w, N–H), 3058 (w, ArH), 2929 (m, CH_2), 2855 (w, C–H), 2222 (w, C≡C), 1639 (m, C=O), 1591 (m, N–H), 1461 (m), 1438 (m), 1397 (m), 1326 (m), 1079 (w), 917 (w), 742 (m), 635 cm^{-1} (w).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.27–1.36 (m, 1 H, H-5), 1.46–1.78 (m, 8 H, H-3, H-4, H-5, H-6, NH_2), 1.92–2.00 (m, 1 H, H-6), 2.83 (virt. dt, ^3J = 10.2 Hz, $^3J \cong {}^3J$ = 3.9 Hz, 1 H, H-2), 3.04 (virt. q, $^3J \cong {}^3J$ = 4.1 Hz, 1 H, H-1), 7.45–7.51 (m, 2 H, H-7′, H-4′), 7.55 (d, ^3J = 7.7 Hz, 1 H, H-5′), 7.59–7.64 (m, 2 H, H-6′, H-3′), 8.60 (dd, ^3J = 8.1 Hz, ^4J = 1.5 Hz, 1 H, H-8′), 8.64 (d, ^4J = 1.7 Hz, 1 H, H-1′).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 21.8 (t, C-5), 24.6 (t, C-4), 30.2 (t, C-6), 32.7 (t, C-3), 37.5 (d, C-1), 51.9 (d, C-2), 83.2 (s, CHC≡C), 92.0 (s, CHC≡C), 122.2 (s, C-2′), 126.1 (d, C-5′), 126.2 (d, C-4′), 126.6 (d, C-7′), 129.1 (s, C-8a′), 129.2 (s, C-1a′), 130.1 (d, C-8′), 132.5 (d, C-6′), 133.0 (d, C-1′), 135.0 (d, C-3′), 136.6 (s, C-4a′), 137.0 (s, C-5a′), 179.5 (s, C=O).

MS (EI, 70 eV): m/z (%) = 333 (100 [M]$^+$), 290 (89, $[C_{19}H_{14}OS]^+$), 237 (89, $[C_{15}H_9OS]^+$), 139 (11, $[C_7H_7OS]^+$).

HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{21}H_{20}NOS$: 334.1260; found: 334.1259.

1-[3″,5″-Bis(trifluoromethyl)phenyl]-3-{(1*S*,2*S*)-2-[(9′-oxo-9′*H*-thioxanthen-2′-yl)ethynyl]cyclohexyl}thiourea (4)

To a solution of amine **32** (240 mg, 730 µmol, 1.00 equiv) in THF (11 mL) was added isothiocyanate **13** (145 µL, 214 mg, 791 µmol, 1.10 equiv) and the reaction mixture was stirred for 16 h at rt. Then, the solvent was removed under reduced pressure and the crude product was purified by flash chromatography (3 × 15 cm, Chx/EtOAc 9:1 → 4:1). The product **4** was isolated as a bright yellow solid (330 mg, 550 µmol, 74%); mp 201–202 °C; R_f = 0. 43 (Chx/EtOAc 4:1) [UV, $KMnO_4$]; $[\alpha]_D^{20}$ –104 (*c* = 1.00, CH_2Cl_2).

IR (ATR): 3327 (br w, N–H), 3061 (w, ArH), 2934 (w, CH_2), 2858 (w, C–H), 2223 (w, C≡C), 1618 (m, C=O), 1585 (m, N–H), 1523 (m, N–H), 1276 (m, C–F), 1172 (s, C=S), 1128 (s), 986 (m), 884 (m), 744 (m), 681 cm^{-1} (m).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.40–1.50 (m, 1 H, H-5), 1.59–1.67 (m, 2 H, H-4), 1.67–1.73 (m, 1 H, H-3), 1.77 (td, ^3J = 12.4 Hz, 3.8 Hz, 1 H, H-6), 1.82–1.88 (m, 1 H, H-5), 1.95–2.01 (m, 1 H, H-3), 2.06–2.12 (m, 1 H, H-6), 3.48 (virt. q, $^3J \cong {}^3J$ = 4.0 Hz, 1 H, H-2), 4.65 (virt. ddt, ^3J = 11.8 Hz, 7.7 Hz, $^3J \cong {}^3J$ = 3.5 Hz, 1 H, H-1), 7.04 (d, ^3J = 7.7 Hz, 1 H, H-3′), 7.12 (d, ^3J = 8.3 Hz, 1 H, H-4′), 7.38 (d, ^3J = 8.7 Hz, 1 H, cyclohexyl-N*H*CS), 7.49–7.54 (m, 2 H, H-5′, H-4″), 7.58 (dd, ^3J = 8.1 Hz, ^4J = 0.7 Hz, 1 H, H-7′), 7.66 (ddd, ^3J = 8.3 Hz, 7.0 Hz, 1.3 Hz, 1 H, H-6′), 7.99 (br s, 2 H, H-2″, H-6″), 8.32 (d, ^4J = 1.6 Hz, 1 H, H-1′), 8.50 (dd, ^3J = 8.2 Hz, ^4J = 1.3 Hz, 1 H, H-8′), 9.11 (s, 1 H, Ar-N*H*CS).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 21.1 (t, C-4), 25.1 (t, C-5), 28.6 (t, C-6), 30.3 (t, C-3), 33.5 (d, C-2), 54.9 (d, C-1), 83.2 (s, CHC≡*C*), 91.4 (s, CH*C*≡C), 118.4 (d, C-4″), 121.7 (s, C-2′), 123.7 (d, C-2″), 123.8 (d, C-6″), 124.5 (s, CF_3), 125.7 (d, C-4′), 126.3 (d, C-7′), 127.0 (d, C-5′), 128.3 (s, C-1a′), 128.6 (s, C-8a′), 129.8 (d, C-8′), 131.6 (s, C-3″), 132.0 (s, CF_3), 132.3 (s, C-5″), 132.5 (d, C-1′), 133.1 (d, C-6′), 134.8 (d, C-3′), 137.0 (s, C-4a′), 137.6 (s, C-5a′), 140.4 (s, C-1″), 180.0 (s, C=S), 180.3 (s, C=O).

MS (ESI): *m*/*z* = 622 $[M + NH_4]^+$.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{30}H_{23}F_6N_2OS_2$: 605.1151; found: 605.1149.

8-Bromo-2,2,9b-trimethyl-2,3,4a,9b-tetrahydro-1*H*-dibenzofuran-4-one (34)

2-(4-Bromophenoxy)-3,5,5-trimethyl-2-cyclohexen-1-one (**33**; 30.6 mg, 100 µmol, 1.00 equiv) was irradiated together with thiourea **4** (6.04 mg, 10.0 µmol, 0.10 equiv) in a solution of CH_2Cl_2 (*c* = 20 mM) at λ = 419 nm for 24 h at rt. The reaction was stopped, all volatiles were removed under reduced pressure, and the crude product was purified by flash chromatography (2 × 15 cm, Pn/Et_2O 4:1 → 2:1). The title compound was isolated as a yellowish oil (8.1 mg, 26.0 µmol, 26%, 12% *ee*) together with residual starting material (15.8 mg, 51.0 µmol, 54%); R_f = 0.38 (Pn/Et_2O 2:1) [CAM]; $[\alpha]_D^{20}$ +10 (*c* = 1.00, CH_2Cl_2).

Chiral HPLC (AD-H, 250 × 4.6 mm, *n*-heptane/*i*-PrOH (90:10), 1 mL/min, λ = 210 nm, 254 nm): t_R (racemate) = 10.3 min (**34**), 13.2 min (*ent*-**34**).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.61 [s, 3 H, C-2(CH_3)], 1.11 [s, 3 H, C-2(CH_3)], 1.40 [s, 3 H, C-9b(CH_3)], 1.95 (d, ^2J = 14.8 Hz, 1 H, C*H*H-1), 2.19–2.24 (m, 2 H, CH*H*-1, C*H*H-3), 2.37 (d, ^2J = 12.7 Hz, 1 H, CH*H*-3), 4.54 (s, 1 H, H-4a), 6.83 (d, ^3J = 8.5 Hz, 1 H, H_{Ar}), 7.13 (d, ^4J = 2.1 Hz, 1 H, H_{Ar}), 7.24 (dd, ^3J = 8.5 Hz, ^4J = 2.1 Hz, 1 H, H_{Ar}).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 27.1 [q, C-2(CH_3)], 32.4 [q, C-2(CH_3)], 32.4 [q, C-9b(CH_3)], 36.1 (s, C-2), 46.0 (t, C-1), 49.6 (s, C-9b), 51.8 (t, C-3), 91.1 (d, C-4a), 112.4 (d, Car), 113.5 (s, Car), 125.1 (d, Car), 131.4 (d, Car), 136.9 (s, Car), 157.0 (s, Car), 207.2 (s, C-4).

The spectroscopic data match the literature values.[3h]

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