Synthesis of Chiral Thiourea-Thioxanthone Hybrids

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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 thiouazole 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, thioxanthone

Thioxanthone (9H-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 benzene² and thioxanthone has consequently been employed as a triplet sensitizer for several applications.³ Recent interest in visible-light-induced enantioselective transformations³ 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.³⁶ 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 linker.⁷

In light of the spectacular success the thiourea binding motif has encountered in organocatalysis,⁸ 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] photocycloaddition¹⁰ 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.³ 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-
methyl)phenyl isothiocyanate 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. 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, which was to be linked to an appropriately N-protected carboxylic acid derived from enantiopure compound 6. Initial attempts to employ a benzoxycarbonyl 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. 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). Ester formation proceeded smoothly after activation via the acid chloride and reaction with thioxanthone 9. Attempted reduction of compound 10 with tin(II) chloride or by Pd-catalyzed transfer hydrogenation remained unsuccessful. Gratifyingly, it...
was found that the nitro group could be reduced smoothly with indium in an acidic THF/water mixture. 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 while the use of SOCl₂ and POCl₃ as dehydrating agents failed. Oxazole 12 was obtained in 83% yield and the removal of the phthaloyl protecting group was accomplished by hydrazinolysis. 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 was required (Scheme 4). This goal was accomplished by applying a known enantiotopos-differentiating methanolation reaction to the respective succinic anhydride. 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 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. 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 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 1H NMR spectroscopy at ambient temperature. 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 (Jax) and two small coupling constants due to the axial-equatorial coupling (Jae). Indeed, its precursor 25 showed exactly this pattern with Jax = 13.2 Hz and Jae = 5.2 Hz and Jae = 3.6 Hz. The proton at C2 appeared as a virtual quartet with an average coupling constant of J = 5.2 Hz. Related 1H NMR data were recorded for compounds 23 and 24. However, the situation was different for compound 3. The 1H NMR spectrum revealed for H1 a signal that appeared as virtual tt with two coupling constants of J.
= 8.3 Hz and $J = 4.0$ Hz. While one of the larger signal splittings is due to the coupling to NH, the remaining coupling pattern ($J = 8.3, 4.0, 4.0$ Hz) results from coupling to vicinal protons. Likewise, the proton H2 changed its signal pattern and appeared as a virtual dt with $J = 7.4$ Hz and $J = 4.3$ Hz.

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 ethynyl group. The synthesis of this compound started from hydrochloride 21, which was reduced with LiAlH₄ in THF to furnish amino alcohol 26 in 93% yield (Scheme 7). Upon tert-butylcarbonyl (Boc) protection of the amino group, alcohol 27 was subjected to a Swern oxidation. The resulting aldehyde 28 was converted into the terminal alkyne 29 by Seyferth–Gilbert homologization. Sonogashira cross-coupling with the known 2-bromothioxanthone (30) 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 dt with coupling constants of $J = 12.4$ Hz, $J = 8.5$ Hz, and $J = 3.9$ Hz. Since the coupling constant of $J = 8.5$ Hz could be clearly assigned to the vicinal CH–NH coupling the other coupling constants are due to vicinal CH–CH coupling with $J_{ax} = 12.4$ Hz and $J_{eq} = 3.9$ Hz. Likewise, the equatorial proton H2 shows a virtual quartet with $J_{ax} = J_{eq} = 3.6$ Hz.

The UV/Vis spectra of the new thioxanthones are all similar (see the Supporting Information) and the spectrum of compound 4 is representatively shown in Figure 2. The long-wavelength absorption between 370 and 420 nm with a $\lambda_{max} = 392$ 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.
received increasing attention. 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](image)

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 thiourea 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, CHCl₃, and Et₂O were purified using a SPS-800 in flame-dried glassware under positive pressure of argon with magnetic stirring. THF, CH₂Cl₂, and Et₂O were purified using a SPS-800.

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

(1R,2R)-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 NEt₃ (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 CH₂Cl₂ (3 × 100 mL). The combined organic layers were dried (Na₂SO₄) 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; [α]D=20 – 10 (c = 1.00, CHCl₃).

IR (ATR): 3154 (m, OH), 3369 (w, OH), 2936 (m, CH₃), 2861 (m, CH₂), 1740 (w, CO), 1697 (m, C=O), 1600 (w, C=O), 1488 (m, CH₂), 1395 (m, CH₃), 1376 (m), 1310 (w), 1204 (w), 1077 (m), 783 cm⁻¹ (m).

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1H NMR (400 MHz, CDCl₃); δ = 1.50–1.56 (m, 2 H, H-4, H-5), 1.78 (vitr. td, J = 8.6–8.8 Hz), 1.83 (m, 1 H, H-6), 2.00–2.04 (m, 4 H, H-4, H-5, H-6), 2.30 (vitr. qd, J = 1.2 Hz, J = 2.8 Hz, 1 H, H-1), 2.49 (vitr. td, J = 12.8 Hz, J = 13.7 Hz, 1 H, H-3), 3.35 (dd, J = 12.3 Hz, 11.3 Hz, 3 H, H-1, H-6), 3.45 (ddd, J = 12.3 Hz, 11.3 Hz, 4.0 Hz, 1 H, H-2), 7.17 (s, 1 H, H-5), 7.54–7.58 (m, 2 H, H-1, H-6), 7.69 (dd, J = 8.3 Hz, 7.0 Hz, J = 1.6 Hz, 1 H, H-6), 7.74 (dd, J = 8.3 Hz, 7.0 Hz, J = 3.1 Hz, 2 H, H-2, H-5), 7.87 (dd, J = 5.5 Hz, J = 3.1 Hz, 1 H, H-2, H-4), 8.54–8.60 (m, 1 H, H-8), 9.20 (s, 1 H, H-1).

13C NMR (100 MHz, CDCl₃); 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, C-2, 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, C-11′), 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, C-1′, C-3′), 170.9 (s, COO), 177.9 (s, C-9′).

ES (El, 70 eV); m/z (%) = 528 (M⁺), 273 (29, [C₁₅H₁₄NO₃]⁺), 256 (100, [C₁₂H₁₀NO₃]⁺), 148 (79, [C₉H₆NO₂]⁺).

HRMS (EI): m/z [M⁺] calc for C₈H₁₀NO₃S: 256.0959; found: 256.0959.

(1R,2R)-2-[(1′,3′-Dioxoisooindolin-2′-yl)-N-(3′-hydroxy-9′-oxo-9′H-thioxanthone-2′-yl)cyclohexane-1-carboxamide (11)

Ester 10 (406 mg, 768 µmol, 1.00 equiv) was dissolved in THF (27 mL) and H₂O (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 washed with aq NaHCO₃ (100 mL). The aqueous layer was extracted with CH₂Cl₂ (3 × 100 mL). The combined organic layers were dried (Na₂SO₄), filtered, and the solvent was removed under reduced pressure. Purification by flash chromatography (4 × 2 cm, CH₂Cl₂/MeOH 98:2) afforded the title compound as a yellow solid (220 mg, 458 µmol, 83%).

1H NMR (400 MHz, CDCl₃); 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), 2.24–2.45 (m, 2 H, H-3, H-6), 4.12 (dd, J = 12.8 Hz, 11.4 Hz, 3.6 Hz, 1 H, H-2), 4.57 (vitr. td, J = 11.7 Hz, J = 3.8 Hz, 1 H, H-1), 7.44 (ddd, J = 8.2 Hz, 6.9 Hz, J = 1.3 Hz, 1 H, H-1), 7.49–7.52 (m, 2 H, H-4, H-5), 7.57 (dd, J = 6.8 Hz, 3.1 Hz, J = 1.5 Hz, 1 H, H-7), 7.64 (dd, J = 6.8 Hz, J = 5.5 Hz, J = 3.0 Hz, 2 H, H-2, H-5), 7.74 (dd, J = 5.5 Hz, J = 3.0 Hz, 2 H, H-2, H-4), 8.55 (dd, J = 8.2 Hz, J = 1.3 Hz, J = 1.5 Hz, 1 H, H-9), 8.76 (s, 1 H, H-11).

13C NMR (100 MHz, CDCl₃); 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-1′), 122.0 (d, C-11′), 123.4 (d, 2 C, C-4′, C-7′), 125.7 (d, C-6′), 126.4 (d, C-6′), 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-3′), 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′), 169.3 (s, C-2′), 179.8 (s, C-10′).

HRMS (ESI): m/z [M + H⁺] calc for C₂₈H₂₈N₂O₅S: 528.1217; found: 528.1217.

1-[3,5′-His(trifluoromethyl)phenyl]-3-(1R,2R)-2-[(1′,3′-dioxoisooindolin-2′-yl)-N-(3′-hydroxy-9′-oxo-9′H-thioxanthone-2′-yl)cyclohexane-1-carboxamide (9)

Oxazole 12 (70.0 mg, 146 µmol, 1.00 equiv) was dissolved in anhyd MeOH (13 mL). Hydrazine hydrate (364 mg, 3.60 mL, 7.29 mmol, 50.00 equiv) was added and the mixture was stirred at rt for 24 h. On removal of the solvent, the residue was dissolved in CH₂Cl₂ and filtered over SiO₂ (1 × 2 cm, CH₂Cl₂/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 isocyanate (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, CH₂Cl₂/MeOH 99:1) afforded the desired thioamide as a yellow solid (29.0 mg, 46.7 µmol, 32% over two steps); mp 124–126 °C; Rf = 0.20 (CH₂Cl₂/MeOH 99:1) [UV, KMeO₃]; [α]D²⁰−180° (c = 1.00, CH₂Cl₂).

IR (ATR): 3296 (w, NH), 3066 (w, OH), 2931 (m, CH₃), 2857 (m, CH₂), 1766 (w, (C=O), 1588 (m, C≡C), 1517 (m, C≡C≡C), 1438 (m, CH₃), 1369 (m), 1294 (w), 1262 (w), 1077 (m), 717 cm⁻¹ (m, CH₂).
123.8 (d, 2, C-2’), 125.9 (d, C-6’), 126.3 (d, C-7”), 128.2 (s, C-4’a), 129.9 (d, C-8’), 132.4 (q, J = 33.6 Hz, 2, C-3’), 132.8 (d, C-9”), 134.9 (s, C-7a), 137.4 (s, C-5’a), 139.9 (s, C-10’a), 140.0 (s, C-3’a), 152.5 (s, C-11’a), 169.3 (s, C-2’), 180.0 (s, C-15), 180.3 (s, NCSN).


15(2S,3R,4R)-3-(1’,3’-Dioctoindolin-2-yl)bicyclo[2.2.1]hept-5-ene-2-carboxylic Acid (16)

The protected amino acid 16 (870 mg, 3.05 mmol, 1.10 equiv) was dissolved in anhyd toluene (150 mL). Subsequently, pthalic anhydride (978 mg, 6.60 mmol, 1.05 equiv) and NEt3 (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 CH2Cl2 (3 × 150 mL). The combined organic layers were dried (Na2SO4), 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%); [α]D20 = +64 (c = 1.00, CH2Cl2).

IR (ATR): 3227 (m, OH), 3059 (w, CH=sp3), 2983 (w, CH3), 2952 (w, CH2 sp3), 1770 (m, C=C), 1402 (m), 1375 (s), 1178 (m), 1158 (m), 872 (m), 714 (s), 695 (s), 662 cm−1 (m).

1H NMR (300 MHz, CDCl3): δ = 1.75 (vbr dt, J = 9.3 Hz, J = 5.7 Hz, 2 H, H-5), 1.92 (vbr dt, J = 9.3 Hz, J = 1.9 Hz, 1 H, H-7), 2.65 (vbr dt, J = 9.3 Hz, J = 1.9 Hz, 1 H, H-7), 3.00 (dd, J = 8.6 Hz, J = 1.4 Hz, 1 H, H-6), 3.26 (vbr s, 1 H, H-3), 3.42 (vbr d, J = 5.7 Hz, 1 H, H-4), 3.82 (dd, J = 8.6 Hz, J = 1.8 Hz, 1 H, H-3), 4.22 (dd, J = 5.6 Hz, J = 2.9 Hz, 1 H, H-6), 6.31 (dd, J = 5.6 Hz, J = 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-4’).

13C NMR (75 MHz, CDCl3): δ = 45.3 (d, C-1), 45.6 (d, C-2), 45.9 (d, C-3), 47.5 (t, C-7), 55.6 (d, C-3’), 122.3 (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’), 138.3 (d, C-5), 138.8 (d, C-6), 168.9 (s, 2 C, C-1’, C-3’), 176.9 (s, COOH).


(1R,2S,3R,4S)-3-(1’,3’-Dioctoindolin-2-yl)bicyclo[2.2.1]heptane-2-carboxylic Acid (17)

The ester 17 (400 mg, 741 mmol, 1.00 equiv) was dissolved in THF (26 mL) and H2O (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, CH2Cl2 (100 mL) was added and the mixture was filtered over Celite. The mixture was washed with aq NaHCO3 (150 mL) and extracted with CH2Cl2 (3 × 100 mL). The combined organic layers were washed with aq 2 M NaOH (150 mL), dried (Na2SO4), and filtered. The solvent was removed under reduced pressure and the product was obtained as a yellow solid (1.48 g, 2.74 mmol, 99.9%); mp 202–206 °C; Rf = 0.83 (CH2Cl2/MeOH 92:8) [UV, KMN0: [α]D20 = -92 (c = 1.00, CH2Cl2).

IR (ATR): 3089 (w, CH=sp3), 2956 (w, CH3), 2880 (w, CH2 sp3), 1759 (s, C=O), 1702 (s, C=O), 1640 (s, C=O), 1338 (s, N=O), 1105 (s, C=O), 730 cm−1 (m, C=S).

1H NMR (400 MHz, CDCl3): δ = 1.45 (d, J = 2.3 Hz, 1 H, H-6a), 1.47 (d, J = 2.3 Hz, 1 H, H-6b), 1.52–1.55 (m, 1 H, H-7), 1.71–1.86 (m, 2 H, H-5a, H-5b), 2.72 (vbr dt, J = 10.9 Hz, J = 2.0 Hz, 1 H, H-7), 2.94 (s, 1 H, H-1’), 3.01 (s, 1 H, H-4’), 3.31 (dd, J = 9.1 Hz, J = 1.6 Hz, 1 H, H-2’), 4.53 (dd, J = 9.1 Hz, J = 1.5 Hz, 1 H, H-3’), 7.05 (s, 1 H, H-4’), 7.50–7.57 (m, 2 H, H-5’, H-6’), 7.64–7.74 (m, 3 H, H-6’, H-5’), 7.84 (dd, J = 5.4 Hz, J = 3.0 Hz, 2 H, H-4’, H-7’), 8.55 (dd, J = 8.0 Hz, J = 1.5 Hz, 1 H, H-8’), 9.19 (s, 1 H, H-1’).

13C NMR (101 MHz, CDCl3): δ = 28.4 (t, C-4’, C-7’), 29.6 (t, C-5’, C-7), 37.9 (t, C-7), 40.1 (d, C-1’), 40.5 (d, C-4’), 53.6 (d, C-5’), 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-9’a), 127.8 (d, C-7’), 128.3 (d, C-1’), 128.5 (s, C-8’a), 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-4’a), 164.0 (s, C-2’a), 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]+ calc for C26H22N2O4S: 540.0993; found: 540.0993.
The amide 18 (523 mg, 1.03 mmol, 1.00 equiv) was dissolved in anhyd THF (73 mL), and PPh₃ (323 mg, 1.23 mmol, 1.20 equiv) and disopropyl azodicarboxylate (249 mg, 0.24 mL, 1.23 mmol, 1.20 equiv) were 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, CH₂Cl₂/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; Rf = 0.21 (CH₂Cl₂/MeOH 99:1) [UV, KMnO₄]: [α]D ~ −40 (c = 1.00, CH₂Cl₂).

IR (ATR): 3281 (m, NH), 3063 (w, CH₂), 2960 (w, CH₃), 2875 (w, CH₂), 2876 (w, CH₃), 1716 (m, C=O), 1712 (m, C=O), 1675 (m, C=O), 1676 (w, C=O), 1655 (m, C=O), 1648 (m, C=O), 1578 (m, C=O), 1512 (m, C=O), 1442 (m, C=O), 1435 (m, C=O), 1302 (s, C=O), 1279 (s, C=O), 1269 (s, C=O), 1261 (s, C=O), 1222 (s, C=O), 1136 (s, C=O), 1100 (s, C=O), 1074 (s, C=O), 1024 (s, C=O), 992 (s, C=O), 970 (s, C=O), 838 (s, C=O), 823 (s, C=O), 766 (s, C=O), 715 (s, C=O), 655 (s, C=O), 648 (s, C=O), 638 (s, C=O).

HRMS (ESI): m/z [M]⁺ calcd for C₉H₁₀NO₂S: 205.0621; found: 205.0623.

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(1R,2S)-2-(1′,3′-Dioxoisindolin-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 NET3 (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 CH2Cl2 (3 × 150 mL). The combined organic layers were dried (Na2SO4) 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; [α]D20 27.5 (t, C-3), 42.9 (d, C-1), 52.8 (d, C-2), 123.8 (d, 2 C, C-4′), 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, [C13H11NO3S]+), 256 (100, [C16H11NO3]+), 148 (75, [C7H7NO2]+), 104 (58, [M-NO]+).

HRMS (EI): m/z [M]+ calcd for C28H20N2O7S: 528.0991; found: 528.0992.

(1R,2S)-2-(1′,3′-Dioxoisindolin-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 H2O (40 mL) was added. To this solution in (780 mg, 6.80 mmol, 5.00 equiv) and conc HCl (1.12 mL) were added. The mixture was stirred at 80 °C and after 18 h, the solution was cooled to rt and CH2Cl2 (50 mL) was added. The mixture was filtered over Celite and washed with aq NaHCO3 (100 mL). The aqueous layer was extracted with CH2Cl2 (3 × 150 mL). The combined organic layers were dried (Na2SO4), filtered, and the solvent was removed under reduced pressure. Purification by flash chromatography (4 × 20 cm, CH2Cl2/MeOH 95:5) afforded the title product as an orange solid (597 mg, 2.75 mmol, 99%); mp 136–138 °C; [α]D20 12.4 mmol, 91%); mp 136–138 °C; Rf = 0.9 (CH2Cl2/MeOH 95:5) [UV, KMOO]: [α]D20 27.9 (t, C-6), 44.0 (d, C-1), 52.8 (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, [C13H11NO3S]+), 256 (100, [C16H11NO3]+), 148 (75, [C7H7NO2]+), 104 (58, [M-NO]+).

HRMS (EI): m/z [M]+ calcd for C37H30N2O8S: 528.0991; found: 528.0992.
2-[(15R,2R)-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, PPh3 (666 mg, 2.54 mmol, 2.20 equiv) and disopropyl 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, CH2Cl2/MeOH 98:2). The desired product was obtained as a yellow solid (510 mg, 1.06 mmol, 89%; mp 95–98 °C; 80%); mp 95–98 °C. 

IR (ATR): 2932 (w, CH sp3), 1637 (m, C=N), 1520 (s, C=C sp2), 1436 (s, CH p3), 1383 (s), 1274 (s), 1174 (s), 1129 (s), 1022 (s), 957 (s), 748 (s), 714 (s), 698 cm−1 (m, C–S–C).

1H NMR (400 MHz, CDCl3): δ = 1.56 (vitr. ddt, J = 13.6 Hz, 9.6 Hz, 6.7 Hz, J^ = 7.4 Hz, 4.7 Hz, 1 H, H-5), 1.71–1.80 (m, 2 H, H-2, H-4), 1.98–2.06 (m, 1 H, H-3), 2.13–2.16 (m, 1 H, H-1), 2.30–2.34 (m, 1 H, H-3), 2.37 (vitr. dtt, J = 13.4 Hz, 14.6 Hz, J^ = 4.1 Hz, 1 H, H-4), 2.88 (vitr. dttq, J = 13.2 Hz, 8.4 Hz, 5.3 Hz, 3.6 Hz, J^ = 3.6 Hz, 2.7 Hz, 1 H, H-3), 3.69–3.71 (m, 1 H, H-2), 4.59 (ddd, J = 13.2 Hz, 5.3 Hz, 3.6 Hz, 1 H, H-1), 5.49 (ddd, J = 8.2 Hz, 6.9 Hz, J^ = 1.4 Hz, 1 H, H-8), 7.57 (ddd, J = 8.2 Hz, 6.9 Hz, 1.4 Hz, 1 H, H-1), 7.67 (ddd, J = 7.3 Hz, 4.7 Hz, H-5”, H-6”, H-7”). 8.63 (ddd, J = 8.7 Hz, 1.4 Hz, 1 H, H-9’). 8.89 (s, 1 H, H-9’).

13C NMR (101 MHz, CDCl3): δ = 21.3 (t, C-5), 25.6 (t, C-4), 26.4 (t, C-4’), 28.5 (t, C-3), 39.1 (d, C-2), 53.2 (d, C-1), 106.6 (d, C-12), 122.0 (d, C-11’), 123.4 (d, 2 C-4”, 2 C-5”), 125.7 (d, 2 C-6”, 2 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, 2 C-2”), 180.0 (s, C-10”).


1-[3”,5”-Bis(trifluoromethyl)-phenyl]-3-[(15R,2R)-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 CH2Cl2 (35 mL) and ethylenediamine (250 mg, 3.30 g, 32.5 mmol, 5.00 equiv). To this solution, 25 mL of 10 M HCl was added dropwise. The solution was stirred for 1 h at –78 °C. Subsequently, a solution of 26 (510 mg, 1.06 mmol, 1.00 equiv) in anhyd CH2Cl2 (25 mL) was added dropwise. The solution was stirred for 1 h at –78 °C. Subsequently, a solution of 27 was obtained as a yellow oil (213 mg, 928 mg mol%, 92%); δ = 0.17 (vitr.(O=C)H, 4.11 [UV, KMnO4]; [α]2520 + 39 (c = 1.00, CH2Cl2). 

1H NMR (500 MHz, CDCl3): 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, (CH3)], 1.52–1.83 (m, 5 H, H-2, H-3, H-5, H-6, OCH3). 3.21 (vitr. tt, J = 11.4 Hz, 1 H, CHOH), 3.34 (ddd, J = 11.9 Hz, J^ = 4.7 Hz, 1 H, (CH2O), 4.04–4.07 (m, 1 H, H-7), 4.77 (dd, J = 9.0 Hz, 1 H, NH).

13C NMR (126 MHz, CDCl3): δ = 21.0 (t, C-5), 23.1 (t, C-4), 24.9 (t, C-3), 28.2 (q, CH3), 30.3 (t, C-6), 43.1 (d, C-2), 45.1 (d, C-1), 63.9 (t, CH2OH), 80.0 (s, C(CH3)), 157.2 (s, NHCO).

The spectroscopic data match the literature values.3a

tert-Butyl [(15R,2R)-2-[Hydroxymethyl]cyclohexyl]carbamate (27)
A solution of oxazole chloride (0.55 g, 824 mg, 6.50 mmol, 1.00 equiv) in CH2Cl2 (16 mL) was cooled to −78 °C before a solution of DMSO (1.38 mL, 152 g, 19.5 mmol, 3.00 equiv) in CH2Cl2 (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 CH2Cl2 (7 mL) was added slowly over 10 min. After an additional 10 min, NEt3 (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 H2O (20 mL). The layers were separated and the aqueous layer was extracted with CH2Cl2 (2 × 20 mL). The combined organic layers were washed successively with aq NaHCO3 (1 × 25 mL) and brine (2 × 15 mL) and dried (Na2SO4). The solvent was 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.

References:

tert-Butyl [15,25]-2-Ethylnyclohexylocarbamate (29)

A solution of dimethyl(diazomethyl)phosphonate (1.90 g, 12.6 mmol, 2.10 equiv) in THF (190 mL) was added slowly. The reaction mixture was stirred for 1 h and was allowed to warm to rt during that time. The reaction was quenched by the addition of aq NH4Cl (2 × 20 mL) and brine (2 × 20 mL). The organic layers were separated and the aqueous layer was extracted with EtOAc (3 × 80 mL). The combined organic layers were successively washed with aq NH4Cl (2 × 250 mL) and brine (2 × 250 mL), dried (Na2SO4), and the volatiles were removed under reduced pressure. The crude product was purified by flash chromatography (4 × 20 cm, Chx/1B224:1645).

tert-Butyl (15,25)-2-[12-Oxo-9'H-thioxanthen-2'-yl]ethynyl)cyclohexylocarbamate (31)

Alkyne 28 (40 mg, 360 μmol, 1.00 equiv) and bromothioxanthone 30** (114 mg, 394 μmol, 1.10 equiv) were dissolved in anhyd THF (18 mL) and freshly distilled NEt3 (18 mL). The solution was degassed three times by the freeze-pump-thaw method. Subsequently, Ph3P-PdCl2 (41.4 mg, 53.8 μmol, 0.10 equiv) and Cul (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 CH2Cl2 (20 mL) and the organic layer was washed successively with aq NH4Cl (2 × 20 mL) and brine (2 × 20 mL). The organic layer was dried (Na2SO4) 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; Rf = 0.16 (Chx/EtOAc 20:1) [UV, KMMO]; [α]D20** = -154 (c = 1.00, CHCl3).

IR (ATR): 3437 (w, N–H), 3309 (w, C–H), 2977 (w, CH3), 2934 (m, CH2), 1702 (s, C=O), 1497 (s, N–H), 1365 (m), 1326 (m), 1079 (w), 917 (w), 743 (m), 635 cm–1 (w).

1H NMR (400 MHz, CDCl3): δ = 1.19–1.38 (m, 1 H, H-5), 1.43 [s, 9 H, C(CH3)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, J = 4.6 Hz, 1 H, H-2), 3.97 (virt. tt, J = 9.1, 4.1 Hz, 1 H, H-1), 5.15–5.31 (m, 1 H, NH), 9.70 (d, J = 4.2 Hz, 1 H, H-CHO).

13C NMR (101 MHz, CDCl3): δ = 22.9 (t, C-3), 23.7 (t, C-5), 23.9 (t, C-4), 28.5 (q, CH3), 29.8 (t, C-6), 48.2 (d, C-1), 52.1 (d, C-2), 79.6 [s, C(CH3)3], 155.5 (s, NHCO), 204.8 (s, CHO).

The spectroscopic data match the literature values.30

IR (ATR): 3964 (w, N–H), 3013 (w, C–H), 2976 (w, CH3), 2933 (m, CH2), 1702 (s, C=O), 1497 (s, N–H), 1365 (m), 1326 (m), 1079 (w), 917 (w), 743 (m), 635 cm–1 (w).

1H NMR (400 MHz, CDCl3): δ = 1.23–1.40 (m, 1 H, H-5), 1.47 [s, 9 H, C(CH3)3], 1.57–1.71 (m, 4 H, H-3, H-4, H-5, 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, J = 9.5 Hz, 1 H, NH), 7.53 (dd, J = 7.2 Hz, J = 1.4 Hz, 1 H, H-4), 7.55 (d, J = 8.4 Hz, 1 H, H-7'), 7.61 (dd, J = 8.1 Hz, J = 1.4 Hz 1 H, H-5'), 7.64–7.66 (m, 2 H, H-3', H-6'), 8.63 (dd, J = 8.1 Hz, J = 1.5 Hz, 1 H, H-8'), 8.66 (d, J = 1.8 Hz, 1 H, H-1').

13C NMR (101 MHz, CDCl3): δ = 63.8 (t, C-4), 67.2 (t, C-3), 69.4 (t, C-2), 81.3 (s, C=O), 117.1 (s, CH2C), 126.1 (d, C-5), 126.2 (d, C-4), 126.7 (d, C-7), 128.8 (s, C=Oa), 129.2 (s, C-1'a), 130.1 (d, C-8'), 132.6 (d, C-6'), 133.1 (d, C-1'), 135.1 (d, C-3'), 136.8 (s, C-4'a), 137.1 (s, C-5'a), 155.3 (s, NHCO), 179.5 (s, C=O).


2-[(15,25)-5-Aminocyclohexyl(ethenyl)-9'H-thioxanthen-9'-one (32)

Boc-protected amine 31 (75 mg, 173 μmol, 1.00 equiv) was dissolved in CH2Cl2 (2 mL) and cooled to 0 °C. TFA (132 μL, 179 μmol, 10.00 equiv) was slowly added and the solution was stirred at rt for 2 h. The reaction was quenched by the addition of H2O (5 mL) and the layers were separated. The aqueous layer was extracted with CH2Cl2 (2 × 5 mL). The combined organic layers were successively washed with aq NaHCO3 (2 × 15 mL) and brine (1 × 15 mL), dried (Na2SO4), and the volatiles were removed under reduced pressure. The crude product was purified by flash column chromatography (2 × 20 cm, CH2Cl2/MeOH 9:1 + 1 vol% NH3) [UV, KMnO4]; [α]D24 = 167 (30, [C9H13NO2]+), 123 (27, [C9H13N]+), 106 (27, [C7H15]+), 57 [C4H5]+ calc for C31H22N3O5S: 524.1645; found: 524.1645.
1-[3′,5′-Bis[(trifluoromethyl)phenoxy]-3-(15S,25)-2-{[9′-oxo-9′H-thioxanthen-2′-yl]ethynyl}[cyclohexyl]thioureia (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; Rf = 0.43 (CHx/EtOAc 4:1) [UV, KMnO4]; [α]D20 = +104 (c = 1.00, CH3Cl).

IR (ATR): 3327 (br w, N–H), 3061 (w, ArH), 2934 (w, CH2), 2858 (w, C–H).

1H NMR (500 MHz, CDCl3): δ = 0.49–0.50 (m, 3 H, C-2(CH3)), 1.00–1.02 (3 H, C-2(CH3)); 1.12 (3 H, C-4(CH3)); 1.40–1.50 (m, 2 H, H-5); 1.49–1.60 (m, 2 H, H-5′); 1.59–1.67 (m, 1 H, H-4); 1.77 (td, J = 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, 3 H, H-4, H-4′); 3.49 (t, J = 4.0 Hz, 1 H, H-2); 4.65 (vrt, dtt, J = 11.8 Hz, 7.7 Hz, J = 3.5 Hz, 1 H, H-1′); 7.04 (d, J = 7.7 Hz, 1 H, H-3′); 7.12 (d, J = 8.3 Hz, 1 H, H-4′); 7.38 (d, J = 8.7 Hz, 1 H, cyclohexyl-HC). 

13C NMR (101 MHz, CDCl3): δ = 26.0 (q, C-2(CH3)); 32.4 (q, C-9′(CH3)); 36.1 (C-S); 46.0 (t, C-1); 49.6 (s, C-9′(CH3)); 51.8 (t, C-3); 91.1 (d, C-4α); 112.4 (d, C-6); 113.5 (s, C-5′); 121.5 (d, C-4′); 131.3 (d, C-5′′); 136.9 (s, C-Ar); 131.9 (d, C-4); 133.2 (C-5′′); 133.5 (C-1′′); 133.1 (d, C-6′); 136.8 (s, C-5-Ar); 140.4 (s, C-5′′′); 180.0 (C-2, C-4′′′); 180.3 (s, C=O).


2-Bromo-2,2′,9′-trimethyl-2,3,4a,9′-tetrahydro-1H-dibenzo[2000]furan-4-one (34)

2-[(2′-Bromophenoxo)-3,5,5′-trimethyl-2-cyclohexen-1-one (33; 30.6 mg, 100 μmol, 1.00 equiv) was irradiated with thiourea 4 (6.04 mg, 10 μmol, 0.10 equiv) in a solution of CH3Cl (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, Pet/EtOAc 4:1 → 2:1). The title compound was isolated as a yellowish oil (8.1 mg, 26.0 mg, 100% yield). 

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