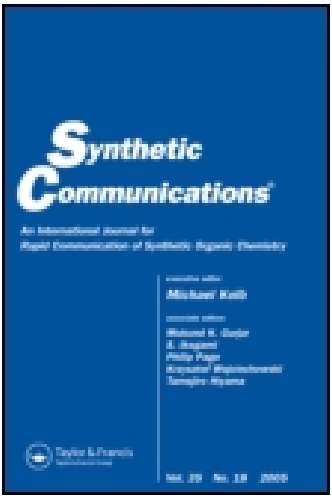

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Synthesis of an Isophorone-Based Nonlinear Optical Chromophore

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ABSTRACT

The synthesis of a "CLD-type" nonlinear optical chromophore incorporating the isophorone unit to rigidize the polyene segment is described. The synthesis required seven steps with an overall yield of 17%.

Key Words: Aldol; Dyes; Knoevenagel; Nonlinear optical; Vilsmeier.

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As part of a project to develop a second-order nonlinear optical polymer for an optical modulator application,[1,2] we required the chromophores **9a**,**9b** (Fig. 1). Structurally similar isophorone-based nonlinear optical chromophores have been prepared;[3] however, one free hydroxyl group on the dialkylamino moiety was necessary for further transformations (to be published elsewhere).

To start out, commercially available **1** was esterified with acetic anhydride catalyzed by base to give the acetate **2** quantitatively (Sch. 1). The acetate protection is required for the subsequent Vilsmeier-Haack formylation,[4] which proceeded smoothly to give **3** in good yield. Next, Knoevenagel reaction of **3** and isophorone was conducted in the presence of a cationic surfactant.[5–7] The hydrolysis of the acetate occurs initially so an extra equivalent of base was required. Although the reaction was slow with moderate yield, compound **4** precipitates pure from the aqueous work-up, making chromatography unnecessary.

Silyl ether protection gave **5** for subsequent Wittig directed-aldol reaction[8,9] with the acetaldehyde equivalent, *N*-cyclohexyl-acetimine,[10] to give moderate yield of a mixture of *Z* and *E* aldehydes **6a**,**6b**, respectively. The $Z:E$ ratio was 33 : 67 by ^{1}H-nuclear magnetic resonance (NMR). Performing this reaction at -100°C did not increase the amount of *E* product. Separation of **6a**,**6b** by silica gel chromatography could only be

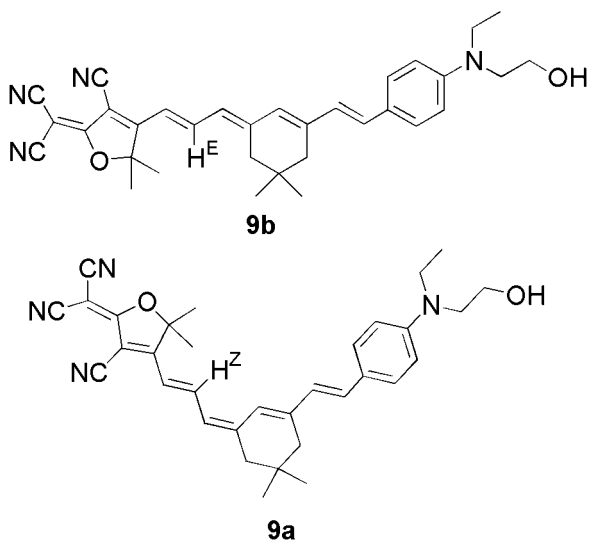
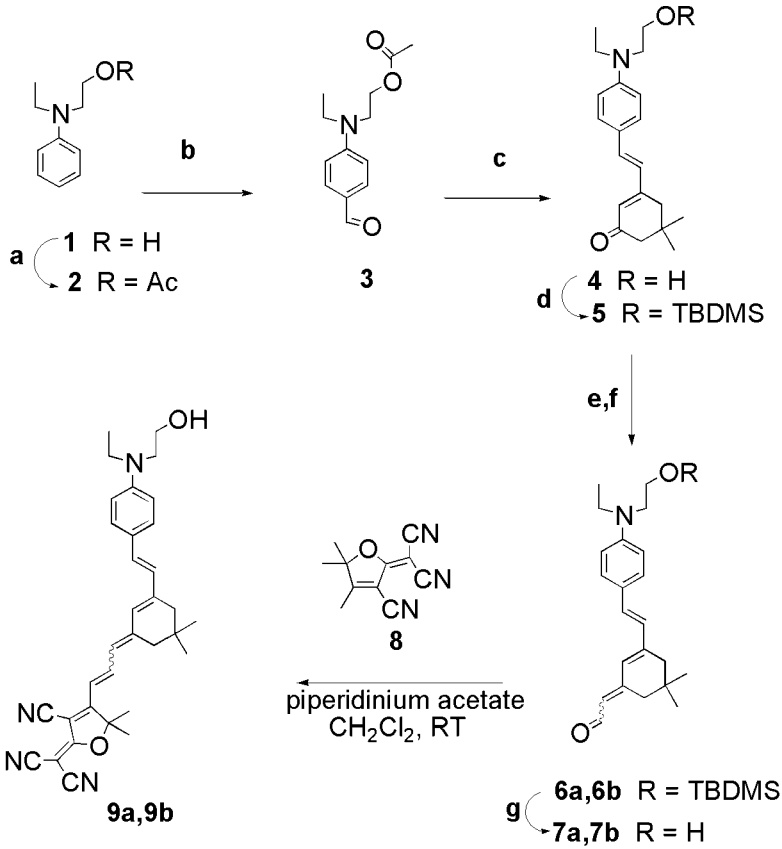


Figure 1. Structure of the chromophores **9a**,**9b**. Protons labelled H^E or H^Z are NMR diagnostic.



Scheme 1. Reagents and conditions: (a) Ac_2O/pyridine; (b) DMF/$POCl_3$; (c) isophorone/cetyltrimethylammonium chloride/NaOH/H_2O/50°C; (d) TBDMSCl/imidazole/dimethylformamide (DMF); (e) N-cyclohexyl-acetimine/lithium diisopropylamide (LDA)/Et_2O, −78 to 0°C; (f) oxalic acid/H_2O; (g) $(Et)_3N^*3HF$/MeCN/40°C.

achieved on analytical scale; therefore, the mixture was used for the subsequent reactions. Deprotection to the aldehyde-alcohols **7a**,**7b** proceeded fast, quantitatively, and without isomerization.

The last step was a Knoevenagel condensation between **7a**,**7b** and the known tricyanodihydrofuran **8**[11] to yield the chromophore mixture **9a**,**9b**. In our hands, the reported preparation of **8** failed to give any product on several attempts. Conditions similar to He et al.[12] provided **8** consistently and in good yield. As a catalyst for the condensation, we chose piperidinium acetate since it has been shown to work well for similar condensations.[13,14]

Investigations of this step with a series of NMR tube reactions demonstrated that the reaction was extremely clean and fast. After scale-up and work-up, the solid that remained appeared perfect by ^{1}H NMR, although quantitative ^{1}H-integration experiments demonstrated purity of only ~85%. Interestingly, the $Z:E$ ratio was 26 : 73, indicating partial isomerization toward the thermodynamically favored *trans* olefin, a phenomenon seen in the preparation of other isophorone-based chromophores.[3,15] After further experimentation, it was found that triturating the solid with acetone gave chromophores **9a**,**9b** as a homogenous crystalline powder. Ignoring some residual CH_2Cl_2 used as solvent for the reaction, the powder had purity of >99% by ^{1}H-NMR corroborated by high-pressure liquid chromatography (HPLC). Combustion analysis showed that **9a**,**9b** cocrystallized with 15% CH_2Cl_2. After 2 months storage, combustion analysis revealed the CH_2Cl_2 had evaporated from the crystalline product.

In summary, we report the synthesis of the nonlinear optical chromophore **9a**,**9b** in seven steps with 17% overall yield.

EXPERIMENTAL

Reagents were purchased from Aldrich Chemical Co. (Milwaukee, WI, USA) and used as received. Multinuclear NMR spectra were obtained on a Bruker AC-200 spectrometer (^{1}H at 200 MHz, ^{13}C at 50 MHz) and referenced to solvent or tetramethylsilane. Piperidinium acetate was prepared by the addition of 1 equivalent glacial HOAc to a cold Et_2O solution of piperidine and suction filtration of the product. *N*-Cyclohexyl-acetimine was prepared as previously described.[10] Melting points were determined on an electrothermal capillary melting point apparatus and are not corrected.

Quantitative ^{1}H-integration experiments were conducted on CD_2Cl_2 solutions with 4,4′-dimethoxyoctafluoro-biphenyl as internal standard using a Bruker AMX-400 (400 MHz ^{1}H). Preparative HPLC was performed using a Shimadzu LC-10AD pump equipped with a Waters 991 diode array detector, an Alltech Econosphere column (250 × 10 mm, 10 μm particle size), and a Gilson CPR fraction collector in order to obtain a purified reference material of chromophore **9a**,**9b**. The reference material was analyzed using a Finnigan Surveyor HPLC, Prevail Silica column (50 × 2.1 mm, 3 μm particle size), and both a diode array detector and a Finnigan LCQ DecaXP Plus mass spectrometric detector used in atmospheric pressure chemical ionization negative ion mode. Quantitation in the visible spectrum was performed at 650 nm. Quantitation by mass spectrum used the (M-1) ion at 519 Da. Burdick and Jackson HPLC grade acetonitrile was used as the eluent for all HPLC analyses.

N-Ethyl-*N*-(2-acetoxyethyl)-aniline (2)

A solution of 82.6 g (2-(*N*-ethylanilino)ethanol (**1**) (0.5 mol) and 39.5 g pyridine (40 mL, 1 equiv) in 300 mL of Et_2O was stirred in an ice bath while 53.6 g acetic anhydride (49.5 mL, 0.53 mol, 1.05 equiv) was slowly added over 15 min. The ice bath was removed and the reaction mixture was heated at reflux for 2 hr. The organic layer was washed with H_2O (3×300 mL) followed by 1% HCl (300 mL). The organic layer was dried ($MgSO_4$), filtered, and evaporated at reduced pressure to provide 92 g (89% yield) of the title compound as a pale yellow liquid. The product was sufficiently pure to use in the subsequent reaction. The crude product can be distilled at reduced pressure, residual pyridine comes over at 75°C 1 mm Hg, product distills at 125°C 1 mm Hg to obtain a colorless liquid. NMR δ_H ($CDCl_3$) 7.29–7.17 (m, 2H), 6.78–6.64 (m, 3H), 4.24 (t, $J = 6.6$ Hz, 2H), 3.56 (t, $J = 6.6$ Hz, 2H), 3.41 (q, $J = 7.0$ Hz, 2H), 2.06 (s, 3H), 1.18 (t, $J = 6.9$ Hz, 3H); δ_C ($CDCl_3$) 170.89, 147.62, 129.36, 116.24, 112.01, 103.51, 61.71, 48.82, 45.21, 20.85, 12.25.

4-Formyl-*N*-ethyl-*N*-(2-acetoxyethyl)-aniline (3)

To 200 mL anhydrous DMF (188.8 g, 2.58 mol, 5.34 equiv) at room temperature was added drop-wise 110 mL $POCl_3$ (181.5 g, 1.18 mol, 2.44 equiv) and then the mixture was stirred for 1.5 hr. Next, 100 g **2** (483 mmol) dissolved in 250 mL of 1,2-dichloroethane was added drop-wise, then the mixture was stirred and heated at 85°C for 8 hr. The reaction mixture was cooled to room temperature and poured into 2 L H_2O and stirred 2 hr then neutralized with a saturated aqueous K_2CO_3. The solution was extracted with $CHCl_3$ (3×600 mL). The combined extracts were washed with H_2O (5×500 mL), dried ($MgSO_4$), and evaporated to yield 95 g of the title compound as a yellow oil (84%). The product was sufficiently pure to use in the subsequent reaction. NMR δ_H (CDCl3) 9.67 (s, 1H), 7.65 (d, $J = 9.0$ Hz, 2H), 6.68 (d, $J = 9.0$ Hz, 2H), 4.19 (t, $J = 6.3$ Hz, 2H), 3.58 (t, $J = 6.3$ Hz, 2H), 3.42 (q, $J = 7.2$ Hz, 2H), 1.97 (s, 3H), 1.15 (t, $J = 7.2$ Hz, 3H); δ_C ($CDCl_3$) 190.10, 170.89, 152.38, 132.24, 125.49, 111.05, 61.23, 48.70, 45.59, 20.89, 12.15.

3-[4-[*N*-Ethyl-*N*-(2-hydroxyethyl)amino]styryl]-5,5-dimethylcyclohex-2-enone (4)

To a mixture of 50 g **3** (213 mmol), 71.3 g isophorone (512 mmol, 2.4 equiv), 330 g 25 wt% cetyltrimethylammonium chloride in H_2O (258 mmol,

1.2 equiv) was added in one portion a solution of 17 g NaOH in 1.7 L H_2O (2 equiv). This mixture was then magnetically stirred and heated to 60°C for 96 hr. After 48 hr a yellowish oil had separated from the mixture. Then 2 L ice water was poured into the reaction followed by 17.6 mL conc. HCl (1 equiv), and any excess acid was neutralized by addition of sodium bicarbonate. After stirring 2 d the yellow precipitated product was filtered, washed with H_2O, and suction dried (32 g, 48%). The product was sufficiently pure to use in the subsequent reaction. m.p. 95°C (shrinks) 107–110°C; NMR δ_H ($CDCl_3$) 7.33 (d, $J = 8.9$ Hz, 2H), 6.76 (AB quart, 2H), 6.68 (d, $J = 8.5$ Hz, 2H), 5.95 (s, 1H), 3.85–3.73 (m, 2H), 3.52–3.36 (overlapping q and t, 4H), 2.41 (s, 2H), 2.24 (s, 2H), 1.81 (bs, OH), 1.15 (t, $J = 7$ Hz, 3H), 1.05 (s, 6H); δ_C ($CDCl_3$) 200.49, 156.36, 149.16, 135.77, 129.15, 125.09, 124.82, 124.12, 112.27, 60.25, 52.50, 51.56, 45.69, 39.29, 33.45, 28.70, 12.19.

3-[4-[*N*-Ethyl-*N*-(2-*tert*-butyldimethylsiloxyethyl)amino]-styryl]-5,5-dimethylcyclohex-2-enone (5)

To a solution of 9.27 g **4** (29.6 mmol) and 5.37 g *tert*-butyldimethylsilyl chloride (35.5 mmol, 1.2 equiv) in 60 mL anhydrous DMF was added 2.43 g imidazole (35.6 mmol, 1.2 equiv), and the reaction was stirred overnight at room temperature. The reaction was then poured into 500 mL ice water and extracted with Et_2O (3 × 150 mL). The extracts were collected, washed with dilute Na_2CO_3, followed by a wash with brine. The extracts were then dried ($MgSO_4$), filtered, and evaporated. The resulting oil was heated at 40 C° for 18 hr under vacuum (0.1 mm Hg) to provide 11.76 g (93%) of the title compound as a viscous red oil. The product was sufficiently pure to use in the subsequent reaction. NMR ($CDCl_3$) 7.36 (d, $J = 8.9$ Hz, 2H), 6.99–6.60 (m, 4H), 6.00 (s, 1H), 3.77 (t, $J = 6.1$ Hz, 2H), 3.53–3.37 (m, 4H), 2.46 (s, 2H), 2.89 (s, 2H), 1.18 (t, $J = 6.9$ Hz, 3H), 1.10 (s, 6H), 0.89 (s, 9H), 0.37 (s, 6H); δ_C ($CDCl_3$) 200.09, 156.10, 148.83, 135.74, 129.08, 124.97, 124.40, 123.49, 111.67, 60.72, 52.51, 51.56, 45.64, 39.20, 33.38, 28.65, 26.02, 18.37, 12.32, −5.24.

2*EZ*-[3-[(1*E*)-2-[4-[*N*-Ethyl-*N*-(2-*tert*-butyldimethylsiloxyethyl)amino]phenyl]-ethenyl]-5,5-dimethyl-2-cyclohexen-1-ylidene]-acetaldehyde (6a(*Z*),6b(*E*))

To 400 mL dry Et_2O under N_2 in a 3-L three-neck flask, cooled in an ice bath, was added 141 mL 2*M* lithium diisopropylamide solution (282 mmol, 1.5 equiv). Then 33 g *N*-cyclohexyl-acetimine (263 mmol, 1.4 equiv) was

added drop-wise, and the solution was stirred for 30 min 0°C. Then the mixture was cooled to −78°C and an addition funnel with a solution of 80.36 g **5** (188 mmol) in 200 mL Et_2O was equipped to the flask. The addition was made in a gentle stream over a period of 30 min. Then the −78°C bath was removed and the flask allowed to warm to room temperature and stirred for 8 hr. The color of the reaction appears dark-greenish during the addition of the ketone and then becomes red-orange after stirring at room temperature. Then the reaction was cooled in an ice bath before 16.2 mL glacial HOAc (282 mmol, 1 equiv relative to lithium amide) was added drop-wise, resulting in a cloudy tomato-orange mixture. Then 26 g oxalic acid (295 mmol) dissolved in 400 mL H_2O was added to the reaction and the mixture was vigorously stirred for 8 hr. The deep-red Et_2O was separated and the aqueous phase extracted again (2 × 200 mL) with Et_2O. The extracts were combined, dried ($MgSO_4$), and rotary evaporated (10 mm Hg, 40°C), leaving a viscous red oil. This oil was dry-column chromatographed (SiO_2; hexanes : EtOAc : MeOH; 9 : 0.8 : 0.2) to provide the title compounds as a red glass (51 g, 60%) as well as some remaining starting ketone. The ratio of the geometric isomers is 68% *Z* and 32% *E* found by integration of their respective aldehydic proton resonances. NMR δ_H ($CDCl_3$) 10.18 (d, $J = 8.2$ Hz, 1H, *Z*), 9.99 (d, $J = 8.2$ Hz, *E*), 7.30 (d, $J = 8.9$ Hz, 2H), 7.29 (d, $J = 8.5$ Hz, 2H), 7.14 (s, 1H, *E*), 6.23 (s, 1H, *Z*), 5.87 (d, $J = 8.6$ Hz, 1H), 2.64 (d, $J = 1.2$ Hz, 2H, *E*), 2.31 (s, 2H), 2.25 (s, 2H *Z*), 1.39 (s, 6H), 1.19 (t, $J = 7.1$ Hz, 3H), 1.02 (s, 6H, *E*), 0.99 (s, 6H, *Z*), 0.85 (s, 9H); δ_C ($CDCl_3$) 190.63, 189.69, 157.18, 156.79, 148.39, 146.90, 146.77, 132.69, 132.58, 128.58, 127.85, 126.17, 125.93, 125.66, 124.20, 124.16, 120.59, 111.77, 60.77, 52.57, 46.45, 45.67, 39.64, 39.33, 39.06, 31.32, 31.21, 28.55, 28.40, 26.07, 18.44, 12.39, −5.27.

2*EZ*-[3-[(1*E*)-2-[4-[*N*-Ethyl-*N*-(2-hydroxyethyl)amino]phenyl]-ethenyl]-5,5-dimethyl-2-cyclohexen-1-ylidene]-acetaldehyde (7a(*Z*),7b(E))

To a magnetically stirred solution of 81 g **6a**,**6b** (179 mmol) in 1 L MeCN was added 29 g triethylamine trihydrofluoride (1 equiv), and the solution was stirred at 40°C for 2 hr. At this time thin-layer chromatography analysis showed no starting material remained. The MeCN was removed by rotary evaporation (10 mm Hg, 40°C) and the dark residue was partitioned between 600 mL CH_2Cl_2 and 200 mL H_2O. The organic phase was separated, dried ($MgSO_4$), and rotary evaporated (10 mm Hg, 40°C). The resulting oil was dry-column chromatographed (SiO_2; hexanes : EtOAc) to provide the title compounds as a deep-red oil (59.2 g, 97%). The ratio of the geometric

isomers is 67% *E*: 33% *Z* found by integration of their respective aldehydic proton resonances. NMR δ_H ($CDCl_3$) 10.21 (d, $J = 7.9$ Hz, *Z*), 10.05 (d, $J = 8.6$ Hz, *E*), 7.36 (d, $J = 9.1$ Hz, 2H, *Z*), 7.35 (d, $J = 9.1$ Hz, 2H, *E*), 7.19 (s, 1H, *E*), 6.79–6.68 (m, 4H), 6.28 (s, 1H, *E*), 5.91 (d, $J = 8.4$ Hz, *E*), 5.71 (d, $J = 9.1$ Hz, *Z*), 3.82 (t, $J = 5.5$, 2H), 3.57–3.40 (m, 4H), 2.68 (d, $J = 1.3$ Hz, 2H, *E*), 2.35 (s, 2H), 2.29 (d, $J = 1.3$ Hz, 2H, *Z*), 1.19 (t, $J = 7$ Hz, 3H), 1.06 (s, 6H, *E*), 1.03 (s, 6H, *Z*); δ_C ($CDCl_3$) 190.87, 189.91, 157.47, 157.11, 148.64, 146.97, 146.78, 132.56, 132.47, 128.61, 128.09, 126.36, 126.25, 126.08, 124.89, 124.23, 120.79, 112.41, 60.32, 52.51, 46.46, 45.70, 39.63, 39.36, 39.05, 31.34, 31.23, 28.54, 28.42, 12.18. Elemental analysis calculated for $C_{22}H_{29}NO_2$: C, 77.83; H, 8.62; N, 4.13. Found: C, 77.27; H, 8.77; N, 4.11.

2-Dicyanomethylene-3-cyano-4,5,5-trimethyl -2,5-dihydrofuran (8)

To 900 mg of sodium ethoxide (13 mmol, 0.15 equiv) dissolved in 10 mL of absolute EtOH in a room temperature water bath was added 9 g 3-hydroxy-3-methyl-2-butanone (88 mmol) and 12 g freshly distilled malononitrile (181 mmol, 2.05 equiv) with stirring. After 1 hr 30 mL of absolute EtOH was added and heated at reflux for 1 additional hr. This is cooled in a refrigerator and the solid filter, washed with a minimal amount of cold EtOH, and then air dryed giving a first crop of 11.6 g of off-white crystalline solid (65% yield). Concentration of the filtrate and cooling gave a second crop of 0.48 g product (total yield 68%). m.p. 199°C–200°C; NMR δ_H ($CDCl_3$) 2.36 (s, 3H), 1.64 (s, 6H); δ_C (DMSO-d_6) 185.59, 177.09, 112.04, 111.32, 109.79, 103.52, 101.17, 54.73, 23.09, 14.06.

[4-[(1*E*,3*EZ*)-3-[3-[(1*E*)-2-[4-[*N*-Ethyl-*N*-(2-hydroxyethyl)amino]phenyl]-ethenyl]-5,5-dimethyl-2-cyclohexen-1-ylidene]-1-propenyl]-3-cyano-5,5-dimethyl-2(5*H*)-furanylidene]-propanedinitrile (9a(*Z*),9b(*E*))

A solution of 5.21 g **7a**,**7b** (15.37 mmol) and 3.06 g **8** (1 equiv) in 150 mL CH_2Cl_2 under N_2 was cooled to 0°C with magnetic stirring in the dark. Then 2.23 g piperidinium acetate (1 equiv) was added in a single portion to the dark-orange solution and the cooling bath was removed. The mixture immediately became dark with a viscous appearance. After 3 hr, thin-layer chromatography (SiO_2; hexanes/EtOAc) showed no starting material remained. Water (50 mL)

was added and a portion of the product precipitated. The entire mixture was filtered through a medium-porosity glass frit, leaving an initial crop of the product as a fine-green crystalline powder. The solid was washed with water, anhydrous acetone and then placed under high vacuum (0.1 mm Hg). The CH_2Cl_2/water mixture was poured into a separatory funnel. After separating the organic layer, it was washed with saturated aqueous $NaHCO_3$ followed by brine. The organic phase was collected, dried ($MgSO_4$), and rotary-evaporated (10 mm Hg, 40°C) to leave a dark-purple, brittle solid. The solid was broken up and slurried at room temperature for 2 hr with 100 mL anhydrous acetone, then filtered to leave the title second crop of title compound as a dark-green, crystalline powder, which was then place under high vacuum (0.1 mm Hg) for several hours. Both crops of product were combined after spectroscopy showed them to be identical (6.7 g total, 85% yield). The ratio of the geometric isomers is 75% *E*: 25% *Z* found by NMR integration (of H^E or H^Z, see Fig. 1). m.p. 231–234°C; NMR δ_H ($CDCl_3$) 8.29 (dd, $J = 14.8$ and 11.6 Hz, *Z*, H^Z), 7.99 (dd, $J = 14.8$ and 11.6 Hz, *E*, H^E), 7.37 (d, $J = 8.9$ Hz, 2H), 6.85–6.77 (m, 2H), 6.73 (d, $J = 8.9$ Hz, 2H), 6.39–6.05 (m, 3H), 3.84 (t, $J = 5.5$ Hz, 2H), 3.53 (t, $J = 5.7$ Hz, 2H), 3.49 (q, $J = 7$ Hz, 2H), 2.47–2.32 (m, 4H), 1.72–1.66 (m, 6H), 1.58 (bs, 1H, OH), 1.20 (t, $J = 7.0$ Hz, 3H), 1.08–1.01 (m, 6H); δ_C (CD_2Cl_2) 176.99, 174.57, 174.12, 155.85, 155.29, 149.62, 149.33, 148.59, 144.63, 143.70, 134.46, 130.16, 129.43, 129.38, 128.36, 126.58, 126.43, 126.06, 125.16, 122.57, 116.19, 115.57, 113.30, 112.78, 112.65, 112.49, 97.75, 97.69, 94.69, 60.75, 55.04, 52.91, 47.49, 46.11, 40.37, 40.15, 39.93, 32.08, 31.85, 28.67, 28.47, 26.89, 12.40. Ignoring residual CH_2Cl_2, quantitative ^1H NMR and HPLC analyses indicated purities of >98% and 99.2%, respectively. Elemental analysis calculated for $C_{33}H_{36}N_4O_2 \cdot 0.15$-$CH_2Cl_2$ (the title compounds cocrystallize with CH_2Cl_2): C, 74.59; H, 6.81; N, 10.5. Found: C, 74.34; H, 6.90; N, 10.46. After 2 months, elemental analysis of this product showed that the CH_2Cl_2 completely evaporated from the crystals after storage at ambient conditions (theory: C, 74.59; H, 6.81; N, 10.5; found: C, 74.34; H, 7.10; N, 10.42).

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