Synthesis of Chiral Thienylpyridines from Naturally Occurring Monoterpenes: Useful Ligands for Cyclometallated Complexes

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On treatment with ammonium acetate, α,β-unsaturated ketones or aldehydes can easily undergo condensation with acetylpyridinium salts (Kröhnke reaction). Four "thienylpyridine" ligands, derived from (−)-β-pinene, (+)-camphor, (+)-3-carene and (+)-2-carene, were prepared according to this method. The multistep syntheses to get (1*R*,5*R*)-3-methylenenopinone **(5)**, (+)-3-methylenecamphor **(10)**, (−)-3-caren-10-al **(15)** and (1*S*,6*R*)-7,7-dimethyl-3-methylenebicyclo[4.1.0]heptan-2-one **(18)** are also described.

Chiral complexes of platinum(II) were first observed with two C^N coordinated 2,6-diphenylpyridines as ligands.[1] A strong distortion of the square planar geometry was observed as a consequence of the steric interaction between the two ligands. However, *cis*-bis[2,6-diphenylpyridine]platinum(II) occurs with both Δ and Λ configurations. Obviously, predetermination of the chirality at the metal center can only be achieved by using ligands that have large steric interactions and are chiral themselves. This goal was reached with the synthesis of (5*R*,7*R*)-5,6,7,8-tetrahydro-9,9-dimethyl-2-(2′-thienyl)-5,7-methanoquinoline, a ligand derived from (−)-α-pinene.[2] *cis*-Bis[(5*R*,7*R*)-5,6,7,8-tetrahydro-9,9-dimethyl-2-(2′-thienyl)-5,7-methanoquinoline]platinum(II) not only shows a large helical distortion, but it also occurs as a pure Δ configured complex.

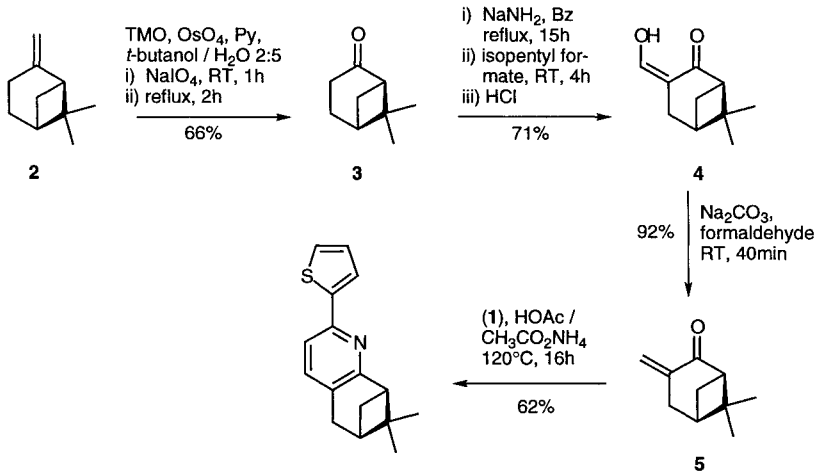
Scheme 1

1

(−)-α-Pinene is not the only natural monoterpene suitable for building chiral, sterically hindered ligands. (−)-β-Pinene, (+)-camphor, (+)-3-carene and (+)-2-carene can easily be converted into α,β-methylene ketones or α,β-ene aldehydes. It is well known that such compounds can undergo condensation with pyridinium salts like **1**.[3] A series of "thienylpyridine" ligands, with aliphatic bicyclic fragments anchored at position 5,6 or 4,5 of the pyridine ring, were prepared. These ligands all have two chiral and two prochiral centers. Their ability to induce a predetermined chirality at the metal center will be the subject of a future study.

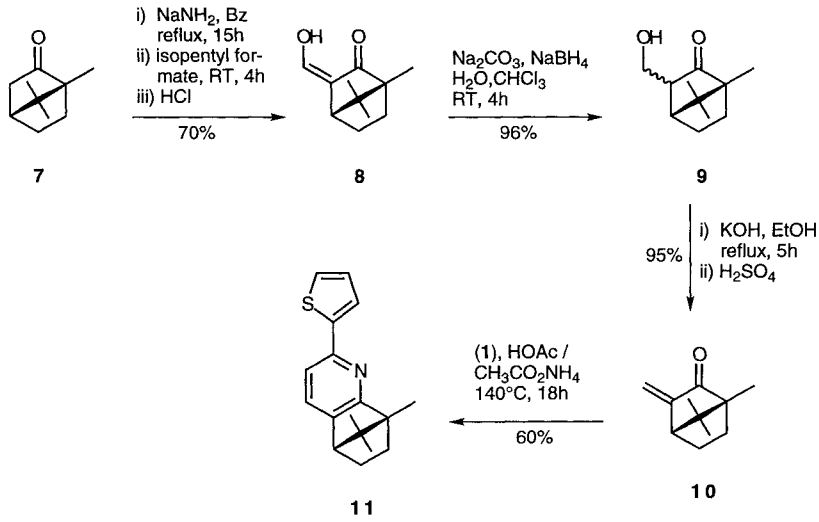
Scheme 1 shows the synthesis of (2-thienylacetyl)pyridinium bromide **(1)**. The first step, bromination of 2-acetylthiophene, was performed by following a modified method of Kipnis.[4] For reasons of instability, 2-bromoacetylthiophene was not isolated but immediately transformed into the pyridinium salt **1** by the addition of pyridine.

Scheme 2 illustrates the pathway followed to obtain ligand **6**. (−)-β-Pinene **(2)** was oxidized into (+)-nopinone **(3)** following one of the three methods described by Brown.[5] Since large-scale ozonolysis can often be hazardous, the one-pot method was preferred. In this reaction, sodium periodate and trimethylamine *N*-oxide dihydrate (TMO) act as cooxidants, while osmium tetroxide is the catalyst. Treatment of **3** with sodium amide gives rise to the formation of an enolate. After addition of isopentyl formate at the α-position, compound **4** and isopentanol are formed on addition of hydrochloric acid. This method has already been used for hydroxymethylenation of men-

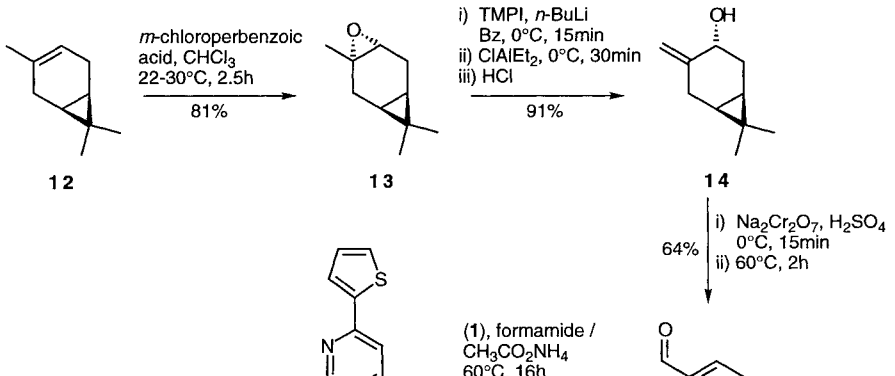


Scheme 2

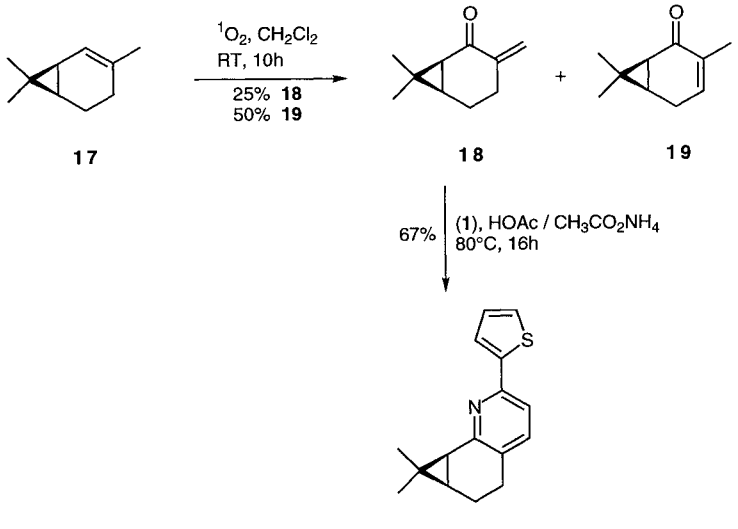
2 **3** **4** **5** **6**



Scheme 3



Scheme 4



Scheme 5

thone,[6] but was modified in order to improve the yield (71%). The α,β-methylene ketone **5** was obtained on treatment with formaldehyde in sodium carbonate solution. Although literature reports many cases where it is possible to isolate spirodioxane intermediates,[7,8] **5** was found to be directly formed in this case. The synthesis of ligand **6** was performed in an acetic acid/ammonium acetate buffer solution. The mechanism for this reaction consists of a Michael addition between **5** and **1**, producing a 1,5-diketone, followed by pyridine elimination and aza ring closure.[1]

The four steps to obtain ligand **11** are represented in Scheme 3. Hydroxymethylenation of (+)-camphor **(7)** was performed, using the same method outlined above with (+)-nopinone **(3)**. This reaction has already been described in many articles, but with disappointing 22–35% yields (70% in our case).[9,10] Hydrogenation of **8** was performed with sodium borohydride.[11] Literature reports that both 3*S*- and 3*R*-isomers are formed in a ratio of 85:15.[10] Elimination of water from the alcohol **9** was performed in a basic solution according to a described method.[12] Ligand **11** was finally formed, in the same way as ligand **6**, by condensation of salt **1** with **10** in an acetic acid/ammonium acetate solution.

Scheme 4 shows the four steps which lead to the formation of ligand **16**. The two possible epoxides from (+)-3-carene **(12)** were prepared by Kuczynski's method.[13,14] α-3,4-Epoxicarane, in which the epoxide and cyclopropane groups are *trans* to each other, can easily be obtained by treatment of **12** with *m*-chloroperbenzoic acid.[15] Opening of the epoxide ring to get alcohol **14** was performed with diethylaluminium tetramethylpiperidine in high yield.[16,17] Conversion of this alcohol into the α-β-ene aldehyde **15** was performed following a synthesis reported by Gollnick and Schade,[18] but the yield (72%) was not reproducible.[17] Compound **15** was obtained with a 75% purity, according to GC analysis, and was used without further purification.

Condensation of **15** with **1** was performed in formamide. Ligand **16** was converted into a pyridinium salt in order to remove the organic impurities and regenerated on basification.

A direct way to synthesize α,β-methylene ketones, which was successfully applied to (−)-α-pinene,[19] is given in Scheme 5. This one-pot reaction, involving photooxidation by singlet oxygen, gave no result with (+)-3-carene **(12)** but partially worked with (+)-2-carene **(17)**. Two methylene ketones, **18** and **19**, were formed in the ratio 1:2. Compound **18** was found to be unstable and to slowly isomerize into **19** on exposure to sunlight. Compound **19**, due to its configuration, cannot undergo an aza ring closure so it is not necessary to separate the two isomers for the synthesis of ligand **20**. The same purification procedure, which was used with **16**, was applied in this case also.

2-Acetylthiophene, (−)-β-pinene **(2)** and (+)-camphor **(7)** were purchased from Fluka; (+)-3-carene **(12)** and (+)-2-carene **(17)** were bought from Aldrich and used without purification. (+)-Nopinone **(3)** was synthesized following the one-pot method of Brown.[5] (+)-3-Hydroxymethylcamphor **(9)**,[10,11] (+)-3-methylenecamphor **(10)**,[10,11,12] (+)-3,4-epoxicarane **(13)**,[15] (−)-7,7-dimethyl-4-methylenebicyclo[4.1.0]heptan-3-ol **(14)**[17] and (−)-3-caren-10-al **(15)**[18] were synthesized following published methods. Anhydrous benzene was purchased from Merck. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded with a Varian Gemini 300 instrument using solvent as the internal standard. Attribution of the proton spectra was performed by COSY and the distinction between carbons types was found using DEPT. IR spectra were collected using a Perkin-Elmer 683 spectrometer. Mass spectra were obtained with a VG Instruments 7070E spectrometer equipped with a FAB inlet system. UV–VIS spectra were recorded on a Perkin-Elmer Lambda 5 spectrometer. Uncorrected melting points were determined with a Buchi 520 apparatus. Microanalyses were obtained from "Ciba–Geigy", Marly, Switzerland.

(2-Thienylacetyl)pyridinium Bromide (1):
2-Acetylthiophene (25.8 g, 204 mmol) in CCl_4 (200 mL) and a catalytic amount of iron filings were heated to 60°C. A solution of Br_2 (32.7 g, 204 mmol) in CCl_4 (100 mL) was slowly added and the mixture stirred for 3 h at 60°C with N_2 bubbling. The reddish solution was filtered through silica gel and the volume reduced to 100 mL. The resulting yellowish solution was cooled in an ice bath and pyridine (40 mL, 497 mmol) was added. The solution was stirred overnight at r.t. and the pyridinium salt **1** was filtered, washed with Et_2O and dried at 80°C under reduced pressure. Yield: 31.9 g (55%).

^{1}H NMR (DMSO-d_6): δ = 9.02 (dd, 2H, ^3J = 6.8 Hz, ^4J = 1.3 Hz), 8.72 (tt, 1H, ^3J = 7.8 Hz, ^4J = 1.3 Hz), 8.27 (dd, 2H, ^3J = 7.8 Hz, ^3J = 6.8 Hz), 8.23 (dd, 1H, ^3J = 4.9 Hz, ^4J = 1.1 Hz), 8.21 (dd, 1H, ^3J = 3.9 Hz, ^4J = 1.1 Hz), 7.41 (dd, 1H, ^3J = 4.9 Hz, ^3J = 3.9 Hz), 6.40 (s, 2H).

^{13}C NMR (DMSO-d_6): δ = 183.6 (q), 146.5 (t), 146.2 (t, 2C), 139.2 (q), 136.8 (t), 135.0 (t), 129.2 (t), 127.8 (t, 2C), 65.6 (s).

Anal. Calc. for $C_{11}H_{10}BrNOS$: C 46.49, H 3.55, N 4.93, Br 28.12; Found C 46,30, H 3.55, N 4.87, Br 28.08.

(1*R*,5*R*)-3-Hydroxymethylene-6,6-dimethylbicyclo[3.1.1]heptan-2-one (4):
(+)-Nopinone (**3**; 10.00 g, 72 mmol) in anhydr. benzene (100 mL) was slowly dropped into a suspension of $NaNH_2$ (5.64 g, 145 mmol) in anhydr. benzene (200 mL) under Ar and heated at 60°C for 15 h. The resulting yellowish solution was cooled in an ice bath and isopentyl formate 90% (8.40 g, 72 mmol) in anhydr. benzene (50 mL) was added. After 4 h of stirring under Ar, the orange product was dissolved in H_2O (400 mL) and two phases separated. The organic phase was extracted with H_2O (2 × 200 mL). The combined aqueous layers were washed with Et_2O (400 mL). The product was acidified with 37% HCl (60 mL), extracted with Et_2O (4 × 200 mL) and dried ($MgSO_4$). After removal of the solvent, the pale yellow oil was found to crystallize at 4°C. Yield: 8.59 g (71%).

^{1}H NMR ($CDCl_3$): δ = 7.17 (s, 1H), 2.42–2.57 (m, 4H), 2.23 (tdd, 1H, ^4J = 5.8 Hz, ^3J = 5.8 Hz, ^3J = 2.9 Hz), 1.39 (d, 1H, ^2J = 10.2 Hz), 1.31 (s, 3H), 0.90 (s, 3H).

(1*R*,5*R*)-6,6-Dimethyl-3-methylenebicyclo[3.1.1]heptan-2-one (5):
A solution of **4** (8.59 g, 52 mmol) in Et_2O (150 mL) was stirred in a suspension of Na_2CO_3 (30.00 g, 535 mmol) in HCHO (37%, 30 mL, 400 mmol) for 40 min. The remaining Na_2CO_3 was dissolved in a minimum amount of H_2O and the two phases separated. The aqueous phase was extracted with Et_2O (3 × 100 mL) and the combined organic solutions were dried ($MgSO_4$). Evaporation of the solvent gave a yellowish liquid which was used without further purification in the next step. Yield: 7.15 (92%).

^{1}H NMR ($CDCl_3$): δ = 6.29 (d, 1H, ^2J = 2.0 Hz), 5.36 (d, 1H, ^2J = 2.0 Hz), 2.69–2.73 (m, 2H), 2.55–2.61 (m, 2H), 2.21 (tdd, 1H, ^4J = 5.9 Hz, ^3J = 5.9 Hz, ^3J = 2.9 Hz), 1.33 (s, 3H), 1.31 (d, 1H, ^2J = 8.1 Hz), 0.85 (s, 3H).

(6*R*,8*R*)-5,6,7,8-Tetrahydro-9-9-dimethyl-2-(2′-thienyl)-6,8-methanoquinoline (6):
(2-Thienylacetyl)pyridinium bromide (**1**; 13.52 g, 48 mmol) in HOAc (50 mL), $CH_3CO_2NH_4$ (29.35 g, 381 mmol) and compound **5** (7.15 g, 48 mmol) were heated at 120°C for 16 h. The reaction

was quenched with H_2O (20 mL) and the black solution was extracted with hexane (8 × 100 mL). After drying ($MgSO_4$), the solvent was removed and a brownish oil isolated. The product was purified by column chromatography (silica gel, CH_2Cl_2/hexane 3:1) and, after removal of the solvent, solidified at r.t. Yield: 7.48 g (62%), mp 94–5°C.

^{1}H NMR ($CDCl_3$): δ = 7.50 (dd, 1 H, ^3J = 3.6 Hz, ^4J = 1.1 Hz), 7.40 (d, 1 H, ^3J = 7.9 Hz), 7.35 (d, 1 H, ^3J = 7.9 Hz), 7.30 (dd, 1 H, ^3J = 5.1 Hz, ^4J = 1.1 Hz), 7.06 (dd, 1 H, ^3J = 5.1 Hz, ^3J = 3.6 Hz), 3.03 (dd, 1, ^3J = 5.8 Hz, ^4J = 5.8 Hz), 2.91 (d, 2 H, ^3J = 2.9 Hz), 2.70 (ddd, 1 H, ^2J = 9.8 Hz, ^3J = 5.8 Hz, ^3J = 5.8 Hz), 2.30 (tdd, 1 H, ^4J = 5.8 Hz, ^3J = 5.8 Hz, ^3J = 2.9 Hz), 1.40 (s, 3 H), 1.28 (d, 1 H, ^2J = 9.8 Hz), 0.69 (s, 3 H).

^{13}C NMR ($CDCl_3$): δ = 166.1 (q), 148.4 (q), 145.3 (q), 135.5 (t), 128.5 (q), 127.7 (t), 126.2 (t), 123.6 (t), 116.4 (t), 50.2 (t), 40.0 (t), 39.0 (q), 31.1 (s), 30.8 (s), 25.9 (p), 21.2 (p).

MS (EI): *m/z* (%) = 255 (M^+, 45), 240 ($M^+ - CH_3$, 21), 226 ($M^+ - C_2H_5$, 7), 212 ($M^+ - C_3H_7$, 100).

IR (KBr): ν = 2926 s, 1578 m, 1448 s, 1416 s, 1258 w, 1216 w, 1140 w, 1104 w, 1016 w, 944 w, 826 s, 724 s cm^{-1}.

UV–VIS (CH_2Cl_2): λ = 266 (sh), 278 (sh), 290 (sh), 312 (14520) nm.

Anal. Calc. for $C_{16}H_{17}NS$: C 75.25, H, 6.71, N 5.48, S 12.55; Found C 75.14, H 6.83, N 5.40, S 12.67.

(1*R*,4*S*)-3-Hydroxymethylene-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one (8):

(+)-Camphor 97% (**7**; 18.83 g, 120 mmol) in anhydr. benzene (50 mL) was slowly dropped into a suspension of $NaNH_2$ (9.36 g, 240 mmol) in anhydr. benzene (200 mL) under Ar and refluxed for 15 h. The resulting orange solution was cooled in an ice bath and 90% isopentyl formate (15.49 g, 120 mmol) in anhydr. benzene (25 mL) was added. After 4 h of stirring under Ar, the orange product was dissolved in H_2O (400 mL) and the two phases separated. The organic phase was extracted with H_2O (2 × 200 mL). The combined aqueous layers were washed with Et_2O (400 mL). The product was acidified with 37% HCl (60 mL), extracted with Et_2O (4 × 200 mL) and dried ($MgSO_4$). After removal of the solvent, the pale yellowish oil was found to crystallize at r.t. Yield: 15.16 g (70%). ^{1}H NMR measurement was in agreement with literature data.[10]

^{1}H NMR ($CDCl_3$): δ = 6.75 (s, 1 H), 2.41 (d, 1 H, ^3J = 3.7 Hz), 1.99 (ddd, 1 H, ^2J = 14.6 Hz, ^3J = 7.3 Hz, ^3J = 3.7 Hz), 1.60–1.72 (m, 1 H), 1.35–1.42 (m, 2 H), 0.94 (s, 3 H), 0.90 (s, 3 H), 0.81 (s, 3 H).

(5*S*,8*R*)-5,6,7,8-Tetrahydro-8,9,9-trimethyl-2-(2′-thienyl)-5,8-methanoquinoline (11):

(2-Thienylacetyl)pyridinium bromide (**1**; 8.86 g, 31 mmol) in HOAc (50 mL), $CH_3CO_2NH_4$ (19.22 g, 250 mmol) and **10** (5.12 g, 31 mmol) were heated at 140°C for 18 h. The reaction was quenched with H_2O (20 mL) and the black solution was extracted with hexane (8 × 100 mL). After drying ($MgSO_4$), the solvent was removed and a brownish oil isolated. The product was purified by column chromatography (silica gel, CH_2Cl_2/hexane 3:1) and, after removal of the solvent, an orange oil was collected. All attempts to crystallize **11** were unsuccessful. Yield: 5.04 g (60%).

^{1}H NMR ($CDCl_3$): δ = 7.52 (dd, 1 H, ^3J = 3.6 Hz, ^4J = 1.1 Hz), 7.32 (s, 2 H), 7.28 (dd, 1 H, ^3J = 5.0 Hz, ^4J = 1.1 Hz), 7.05 (dd, 1 H, ^3J = 5.0 Hz, ^3J = 3.6 Hz), 2.82 (d, 1 H, ^3J = 4.1 Hz), 2.10 (dddd, 1 H, ^2J = 12.0 Hz, ^3J = 6.2 Hz, ^3J = 4.1 Hz, ^3J = 3.8 Hz), 1.85 (ddd, 1 H, ^2J = 12.0 Hz, ^3J = 10.1 Hz, ^3J = 3.7 Hz), 1.34 (s, 3 H), 1.26 (ddd, 1 H, ^2J = 11.7 Hz, ^3J = 6.2 Hz, ^3J = 3.7 Hz), 1.12 (ddd, 1 H, ^2J = 11.7 Hz, ^3J = 10.1 Hz, ^3J = 3.8 Hz), 0.98 (s, 3 H), 0.57 (s, 3 H).

^{13}C NMR ($CDCl_3$): δ = 170.2 (q), 148.9 (q), 146.1 (q), 139.7 (q), 128.3 (t), 127.7 (t), 125.9 (t), 123.2 (t), 115.7 (t), 56.5 (q), 54.1 (q), 51.3 (t), 31.6 (s), 26.1 (s), 20.0 (p), 19.2 (p), 10.2 (p).

MS (EI): *m/z* (%) = 269 (M^+, 26), 254 ($M^+ - CH_3$, 23), 240 ($M^+ - C_2H_5$, 29), 226 ($M^+ - C_3H_7$, 100).

IR (KBr): ν = 2956 s, 2924 m, 1576 m 1444 s, 1414 s, 1280 w, 1166 w, 1120 w, 1084 w, 920 w, 828 m, 698 s cm^{-1}.

UV–VIS (CH_2Cl_2): λ = 312 (16040) nm.

Anal. Calc. for $C_{17}H_{19}NS$: C 75.79, H 7.11, N 5.20, S 11.90; Found C 75.72, H 7.31, N 5.02, S 11.62.

(5a*R*,6a*S*)-5,5a,6a,7-Tetrahydro-6,6-dimethyl-3-(2′-thienyl)cyclopropa[*g*]isoquinoline (16):

2-Thienylacetylpyridinium bromide (**1**; 10.00 g, 36 mmol) in $HCONH_2$ (50 mL), $CH_3CO_2NH_4$ (21.92 g, 284 mmol) and (−)-3-caren-10-al 75% (**15**; 7.12 g, 36 mmol) were heated at 60°C for 16 h. The reaction was quenched with H_2O (20 mL) and the black solution extracted with hexane (8 × 100 mL). The solvent was removed and the product dissolved in Et_2O (100 mL). 2 M HCl was added (200 mL) and the solution vigorously shaken. After separation of the two phases the aqueous solution was neutralized with 25% NH_3. The product was finally extracted with Et_2O (3 × 100 mL) and an orange oil was collected after removal of the solvent. All attempts to crystallize compound **16** failed. Yield: 2.27 g (25%).

^{1}H NMR ($CDCl_3$): δ = 8.24 (s, 1 H), 7.48 (dd, 1 H, ^3J = 3.6 Hz, ^4J = 1.1 Hz), 7.33 (s, 1 H), 7.30 (dd, 1 H, ^3J = 5.0 Hz, ^4J = 1.1 Hz), 7.06 (dd, 1 H, ^3J = 5.0 Hz, ^3J = 3.6 Hz), 3.12 (dd, 1 H, ^2J = 5.0 Hz, ^3J = 3.6 Hz), 3.06 (dd, 1 H, ^2J = 6.9 Hz, ^3J = 4.2 Hz), 2.64–2.68 (m, 1 H), 2.52–2.62 (m, 1 H), 1.09 (s, 3 H), 0.92–0.98 (m, 2 H), 0.75 (s, 3 H).

^{13}C NMR ($CDCl_3$): δ = 149.6 (t), 149.3 (q), 146.1 (q), 145.0 (q), 130.9 (q), 127.8 (t), 126.4 (t), 123.5 (t), 118.4 (t), 28.4 (p), 24.4 (s), 21.4 (s), 19.2 (t), 18.9 (t), 17.8 (q), 14.4 (p).

MS (EI): *m/z* (%) = 255 (M^+, 48), 240 ($M^+ - CH_3$, 31), 226 ($M^+ - C_2H_5$, 9), 212 ($M^+ - C_3H_7$, 100).

IR (KBr): ν = 2934 s, 1658 w, 1596 s, 1536 m, 1472 s, 1430 m, 1390 m, 1212 m, 1124 m, 1052 w, 990 w, 934 w, 854 m, 792 m, 700 s cm^{-1}.

UV–VIS (CH_2Cl_2): λ = 265 (sh), 296 (12560) nm.

Anal. Calc. for $C_{16}H_{17}NS$: C 75.25, H 6.71, N 5.48, S 12.55; Found C 74.96, H 6.85, N 5.38, S 12.65.

(1*S*,6*R*)-7,7-Dimethyl-3-methylenebicyclo[4.1.0]heptan-2-one (18) and (1*S*,6*R*)-3-caren-2-one (19):

(+)-2-Carene 97% (**17**; 15.00 g, 107 mmol), Ac_2O (11.23 g, 110 mmol), pyridine (4.27 g, 54 mmol), tetraphenylporphine (10 mg) and DMAP (240 mg, 2 mmol) were placed in a specialized reaction vessel with O_2 flux and UV irradiation for 14 h. The brownish solution was then diluted in CH_2Cl_2 (200 mL) and washed with sat. $NaHCO_3$ (5 × 100 mL), 1 M HCl (2 × 100 mL), sat. $CuSO_4$ (100 mL) and sat. NaCl (2 × 100 mL). After drying ($MgSO_4$) and removal of the solvent, the resulting orange oil was distilled under vacuum (bp 28°C, 10^{-4} Torr). A colourless liquid was isolated, composed of compounds **18** and **19** in the ratio 1:2. Yield: 12.12 g (76%). This mixture was used without further purification since **19** would not react in the next step. Compound **18** was fully converted into its isomer **19** after one week of exposure to sunlight.

18:

^{1}H NMR ($CDCl_3$): δ = 5.77 (d, 1 H ^2J = 1.8 Hz), 5.06 (d, 1 H, ^2J = 1.8 Hz), 2.44–2.51 (m, 2 H), 2.09–2.17 (m, 1 H), 1.58–1.68 (m, 1 H), 1.50–1.53 (m, 2 H), 1.13 (s, 3 H), 1.04 (s, 3 H).

19:

^{1}H NMR ($CDCl_3$): δ = 6.32–6.37 (m, 1 H), 2.65 (m, 1 H, ^2J = 21.4 Hz), 2.39 (m, 1 H, ^2J = 21.4 Hz), 1.71 (s, 3 H), 1.58 (d, 1 H, ^3J = 8.0 Hz), 1.38 (dd, 1 H, ^3J = 8.0 Hz, ^3J = 8.0 Hz), 1.13 (s, 3 H), 1.02 (s, 3 H).

^{13}C NMR ($CDCl_3$): δ = 196.4 (q), 142.5 (t), 135.0 (q), 34.3 (t), 28.4 (p), 26.3 (t), 23.0 (s), 21.8 (q) 16.0 (p), 14.2 (p).

(6a*R*,7a*S*)-5,6,6a,7a-Tetrahydro-7,7-dimethyl-2-(2′-thienyl)cyclopropa[*h*]quinoline (20):

(2-Thienylacetyl)pyridinium bromide (**1**; 7.34 g, 26 mmol) in HOAc (50 mL), $CH_3CO_2NH_4$ (15.92 g, 206 mmol) and the mixture of compounds **18** and **19** (12.12 g, 81 mmol) were heated at 80°C for 15 h. The reaction was quenched with H_2O (20 mL) and the black solution extracted with hexane (8 × 100 mL). The solvent was removed and the product dissolved in Et_2O (100 mL). 2 M HCl (200 mL) was

added and the solution vigorously shaken. After separation of the two phases, the aqueous solution was neutralized with 25% NH_3. The product was finally extracted with Et_2O (3×100 mL) and an orange oil was collected after removal of the solvent. This oil was diluted in a minimum amount of pentane and, after leaving overnight at -18 °C, a beige precipitate was collected. Yield: 4.40 g (67%), mp 76–7 °C.

^{1}H NMR ($CDCl_3$): $\delta = 7.52$ (dd, 1 H, $^3J = 3.6$ Hz, $^4J = 1.1$ Hz), 7.33 (d, 1 H, $^3J = 8.0$ Hz), 7.31 (dd, 1 H, $^3J = 5.1$ Hz, $^4J = 1.1$ Hz), 7.27 (d, 1 H, $^3J = 8.0$ Hz), 7.06 (dd, 1 H, $^3J = 5.1$ Hz, $^3J = 3.6$ Hz), 2.73 (ddd, 1 H, $^2J = 16.0$ Hz, $^3J = 7.2$ Hz, $^3J = 7.2$ Hz), 2.50 (ddd, 1 H, $^2J = 16.0$ Hz, $^3J = 7.2$ Hz, $^3J = 7.2$ Hz), 1.95–2.08 (m, 2 H), 1.83 (dddd, 1 H, $^2J = 18.1$ Hz, $^3J = 7.2$ Hz, $^3J = 7.2$ Hz, $^3J = 3.7$ Hz), 1.33 (ddd, 1 H, $^3J = 8.4$ Hz, $^3J = 7.2$ Hz, $^3J = 3.7$ Hz), 1.25 (s, 3 H), 0.83 (s, 3 H).

^{13}C NMR ($CDCl_3$): $\delta = 156.8$ (q), 150.1 (q), 145.5 (q), 136.1 (t), 129.9 (q), 127.7 (t), 126.4 (t), 123.8 (t), 116.0 (t), 29.2 (p), 28.5 (t), 28.0 (s), 25.2 (q), 25.1 (t), 18.7 (s), 16.3 (p).

MS (EI): m/z (%) = 255 (M^+, 100), 240 ($M^+ - CH_3$, 81), 226 ($M^+ - C_2H_5$, 11), 212 ($M^+ - C_3H_7$, 53).

IR (KBr): $\nu = 3420$ w, 3066 m, 2992 w, 2926 s, 1586 m, 1568 m, 1458 s, 1432 s, 1264 m, 1122 w, 1064 w, 828 s, 724 m cm^{-1}.

UV–VIS (CH_2Cl_2): $\lambda = 280$ (sh), 289 (9240), 314 (14050) nm.

Anal. Calc. for $C_{16}H_{17}NS$: C 75.25, H 6.71, N 5.48, S 12.55; Found C 75.13, H 6.96, N 5.44, S 12.44.

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