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Atom-Economic Synthesis of Functionalized Octahydroacridines from Citronellal or 3-(Phenylthio)-citronellal

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Atom-Economic Synthesis of Functionalized Octahydroacridines from Citronellal or 3-(Phenylthio)-citronellal

Raquel G. Jacob, Márcio S. Silva, Samuel R. Mendes, Elton L. Borges, Eder J. Lenardão, and Gelson Perin
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Abstract: Here we present a simple, solvent-free, one-pot, hetero-Diels–Alder reaction of (*R*)-citronellal or 3-(phenylthio)-citronellal with arylamines using solid-supported catalyst ($SiO_2/ZnCl_2$). This general, efficient, and improved method is selective, affording preferentially new *trans*-fused 3-(phenylthio)-octahydroacridines (*S*-OHAs) in good yields. The use of microwave irradiation facilitates the procedure and accelerates the reaction.

Keywords: Citronellal, octahydroacridines, solvent-free, supported catalysis

INTRODUCTION

Lewis-acid–catalyzed intramolecular reactions of *N*-arylimines with nonactivated alkenes, formally a hetero-Diels–Alder (HDA) reaction of a 2-azadiene, is a powerful synthetic tool for the preparation of nitrogen-containing six-membered heterocycles.[1] This efficient protocol has been used in the synthesis of several substituted tetrahydroquinoline[2] and octahydroacridine (OHA) derivatives.[3] Among the OHA derivatives, 1,2,3,4,4a,9,9a,10-octahydroacridines are of interest because of

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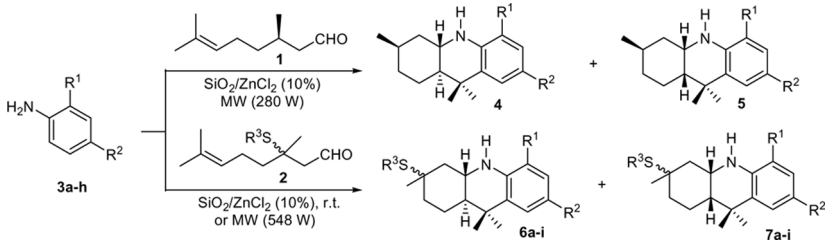


Scheme 1. Synthesis of 3-(phenylthio)-octahydroacridines.

their pharmacological properties, acting as gastric acid secretion inhibitors and antimalarial agents.[4]

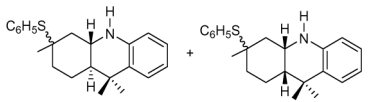
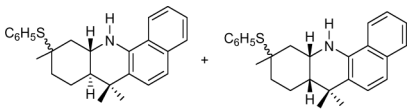
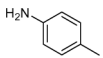
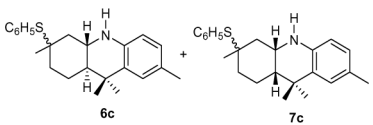
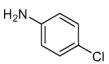
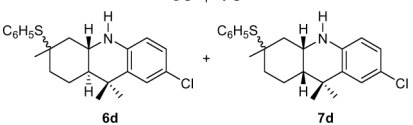
There are a number of different methods for constructing the OHA skeleton, such as acid-catalyzed isophorone-aniline condensation,[5] Beckmann rearrangement of oxime sulfonate,[6] and catalytic hydrogenation of acridine.[7] The imine-Diels–Alder reaction catalyzed by a Lewis-acid is the most atom-economical method, furnishing OHAs in good yields and, in some cases, with 100% of stereoselectivity.[3e] When trifluoroethanol[3f] or an ionic liquid[3g,h] is present, a Lewis acid is not necessary. On the other hand, despite the increasing number of studies showing the useful pharmacological and biological activities of organochalcogenium compounds,[8] the synthesis of phenylthio-octahydroacridines (*S*-OHAs) had not been described.

Our major research goal is the synthesis[3h,9] and application of organochalcogenium compounds, including the development of new, cleaner protocols for classical reactions.[3i,9] In continuation of these studies, we report herein the full results on the imine-Diels–Alder reaction of (*R*)-citronellal **1** or 3-(phenylthio)-citronellals **2** with anilines **3** in the presence of a solid-supported catalyst, under solvent-free conditions, to afford new functionalized OHAs **4** and **5** and 3-(phenylthio)-octahydroacridines **6** and **7** (*S*-OHAs, Scheme 1, Table 1).

RESULTS AND DISCUSSION

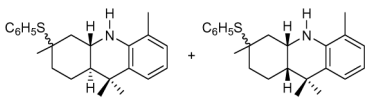
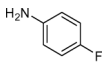
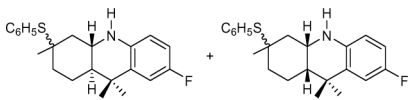
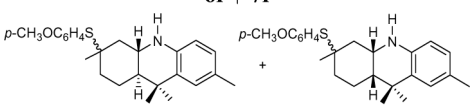
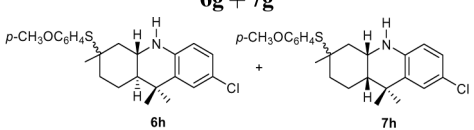
The partial results of the reaction of (*R*)-citronellal **1** and anilines **3** for the synthesis of 1,2,3,4,4a,9,9a,10-octahydroacridines **4** and **5** by a hetero--Diels–Alder reaction were described by us a few years ago.[3i] The method involved the use of solid-supported catalyst ($SiO_2/ZnCl_2$) and afforded selectively a series of OHAs after few minutes of irradiation with microwaves (MW).[10]

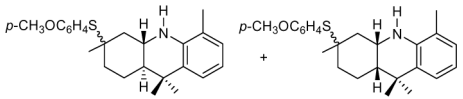
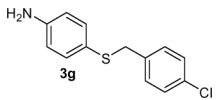
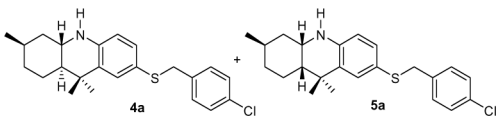
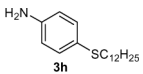
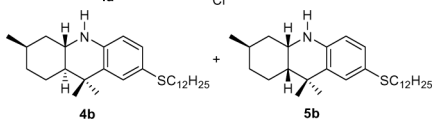
Table 1. Synthesis of 3-(phenylthio)-octahydroacridine derivatives

Entry	Arylamine **3**	Product **6** + **7**	Method[a]	Time	Yields (%)[b]	Ratio[c] **6**:**7** (**6**:**6′**)
1	 **3a**	 **6a** + **7a**	A	3h	74	96:4 (80:20)
2	**3a**	**6a** + **7a**	B	0.5 min	65	90:10
3	**3a**	**6a** + **7a**	C	6 h	82	70:30
4	 **3b**	 **6b** + **7b**	A	1 h	92	39:61 (>99:1)
5	**3b**	**6b** + **7b**	B	0.5 min	88	44:56
6	 **3c**	 **6c** + **7c**	A	3 h	55	95:5 (78:22)
7	3c	**6c** + **7c**	B	1.5 min	52	76:24
8	 **3d**	 **6d** + **7d**	A	4.5 h	65	95:5 (75:25)
9	3d	**6d** + **7d**	B	0.5 min	47	88:12

(*Continued*)

Table 1. Continued

Entry	Arylamine **3**	Product **6** + **7**	Method[a]	Time	Yields (%)[b]	Ratio[c] **6**:**7** (**6**:**6′**)
10	 **3e**	 **6e** + **7e**	A	2.5 h	70	47:53 (>99:1)
11	3e	**6e** + **7e**	B	0.5 min	56	33:67
12	 **3f**	 **6f** + **7f**	A	5 h	70	90:10 (93:7)
13	**3 h**	**6f** + **7f**	B	1.5 min	45	88:12
14	 **3c**	 **6g** + **7g**	A	4.5 h	54	76:24 (98:2)
15	**3c**	**6g** + **7g**	B	1.0 min	48	60:40
16	 **3d**	 **6h** + **7h**	A	5 h	75	95:5 (>99:1)

17	**3d**	**6h + 7h**	B	1.0 min	63	90:10
18	 3e	 6i + 7i	A	3 h	60	37:63 (>99:1)
19	**3e**	**6i + 7i**	B	1.0 min	52	40:60
20	 3g	 4a + 5a	A	5 h	72	56:44[d]
21	 3h	 4b + 5b	A	6 h	65	45:55[d]

[a]Method A: The experiments were performed at room temperature. Method B: The experiments were performed under MW irradiation at 548 W. Method C: Benzene was used as solvent (5 mL/mmol).

[b]Yields of pure products isolated by column chromatography (AcOEt/hexanes) and identified by LRMS, ^{1}H and ^{13}C NMR, and HRMS.

[c]Determined by ^{1}H NMR analysis of the crude reaction mixture and confirmed after isolation of the individual isomers.

[d]Ratio **4**:**5**.

$SiO_2/ZnCl_2$, 10%: Silica gel (9.0 g of silica gel 60, 230–240 mesh, Merck), $ZnCl_2$ (1.0 g) and water (3.0 mL) were mixed in a 50-mL beaker, and the suspension was stirred for 15 min at room temperature, dried at 80°C for 3 h and subsequently 15 h at 150°C in an oven, and finally cooled to room temperature in a desiccator.

In view of the good results using the solid-supported catalyst system in HDA reactions with citronellal and anilines,[3i] we decided to study the preparation of thio-octahydroacridines using our solvent-free approach (Scheme 1, Table 1).

Initially, we performed a study to establish the best conditions for the HDA reaction of 3-(phenylthio)-citronellal (**2a**, $R^3 = C_6H_5$) and aniline (**3a**, $R^1 = R^2 = H$), and we observed that the reaction occurs satisfactorily even at room temperature. Thus, the best results were obtained when a mixture of **2a** (1.0 mmol) and **3a** (1.2 mmol) was stirred in the presence of 0.120 g of $SiO_2/ZnCl_2$ (10%) at room temperature, affording the desired products **6a** and **7a** in good yield (74%) after 3 h (entry 1, Table 1, method A). When the same protocol was performed under irradiation with MW, incomplete consumption of **2a** and **3a** was observed at 280 W, making it necessary to irradiate with 548 W (entry 2, Table 1, method B).

Using the optimized conditions at room temperature, the protocol was extended to other anilines **3** and to 3-(*p*-methoxyphenylthio)-citronellal (**2b**, Table 1). Concerning the stereochemistry of the ring fusion: for all the studied examples, the formation of a *cis* and *trans* mixture of *S*-OHAs (determined by ^{1}H NMR), with good selectivity to the *trans*-*S*-OHAs in most of the examples (entries 1–2, 6–9 and 12–17), was observed. Thus, under our optimized solvent-free conditions, *trans*-**6a** was obtained preferentially in relation to *cis*-**7a** (**6a**:**7a** ratio = 96:4, entry 1, Table 1). This diastereoselectivity is probably due to steric bulk at carbon-3, similar to that described for the intramolecular HDA of 3-methyl-citronellal with *N*-arylimines.[3a] When the reaction was performed in the presence of benzene (5 mL/mmol, method C), the selectivity decreased significantly and the *trans*-**6a**:*cis*-**7a** ratio was 70:30 (entry 3, Table 1). On the other hand, *o*-toluidine **3e** and α-naphtylamine **3b** reacted with aldehydes **2a** and **2b** to afford the respective *cis*-*S*-OHA **7** as the principal diastereomer (entries 4, 5, 10, 11, 18, and 19, Table 1).

We observed almost exclusive formation of one of the two possible *trans*-diastereomeric *S*-OHAs (**6** and **6′**) in all the studied examples. Thus, the diastereomeric ratio of *trans*-*S*-OHAs obtained varied from 75:25 for *trans*-fused 7-chloro-1,2,3,4,4a,9a,10-octahydro-3,9,9-trimethyl-3-(phenylthio)-acridinez (**6d**, method A, entry 8, Table 1) to >99:1 for *trans*-fused 1,2,3,4,4a,9a,10-octahydro-3,5,9,9-tetramethyl-3-(phenylthio)-acridine (**6e**, method A, entry 10, Table 1).

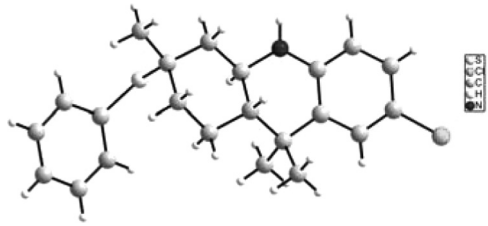


Figure 1. X-ray diagram of the major component of *trans*-**6d**.[11]

These diastereomers were unambiguously characterized by ^{1}H NMR and HRMS, with the relative configuration of the carbon bearing the organosulfur group being determined by x-ray crystal analysis, similar to that described by Laschat and coworkers for OHAs.[11] Figure 1 presents the x-ray diagram of *trans*-**6d** [(3*S**,4a*R**,9a*S**)-7-chloro-1,2,3,4, 4a,9a,10-octahydro-3,9,9-trimethyl-3-(phenylthio)-acridine], the major diastereomer derived from 3-(phenylthio)-citronellal **2a** and *p*-chloroaniline **3d**.

Crystallographic data for **6d** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 663282. Copies of the data can be obtained, free of charge, on application to CCDC. E-mail: deposit@ccdc.ca.ac.uk.

We also performed the HDA reaction using (*R*)-citronellal **1** and thio-functionalized anilines **3g** and **3h**. The reaction occurred satisfactorily at room temperature after stirring a mixture of **1** with **3g** or **3h** in the presence of $SiO_2/ZnCl_2$ (10%) for 5–6 h. In contrast to the observed reaction involving 3-(phenylthio)-citronellal **2** and anilines **3a–c**, the *S*-OHAs **4a–b** and **5a–b** were obtained with poor selectivity (entries 20 and 21, Table 1).

In conclusion, several 3-(phenylthio)-octahydroacridines were directly and stereoselectively prepared by the reaction of 3-(phenylthio)-citronellals with arylamines using solid-supported acid catalyst and solvent-free conditions. This method has low consumption of solvent, short reaction time, mild reaction conditions, and good yields and simplicity, with nonaqueous workup. The reaction time can be reduced under irradiation with MW.

EXPERIMENTAL

General Remarks

The ^{1}H and ^{13}C NMR spectra of $CDCl_3$ solutions were recorded with a 200-MHz or 400-MHz spectrometer (Bruker DPX), as noted. Chemical

shifts are expressed as parts per million (ppm) downfield from tetramethylsilane (TMS) as an internal standard. Low-resolution mass spectra (LRMS, EI) were obtained at 70 eV with a Hewlett Packard EM/CG HP-5988A spectrometer. High-resolution mass spectra (HR-ESI-MS) were obtained in the positive mode (UltrOTOF-Q system, version 1.10, Bruker Daltonics, MA, USA). The MW-irradiated reactions were performed using a Panasonic model Piccolo NN-S42BK operating at 2.45 MHz. Merck's silica gel (230–400 mesh) was used for flash chromatography.

General Procedure for the Synthesis of 3-(Phenylthio)-octahydroacridines 6 and 7

Method A

A mixture of 3-(arylthio)-citronellal[9c] (**2**, 1 mmol) and aniline (**3**, 1 mmol) was added to $SiO_2/ZnCl_2$ (10%) (0.120 g). The mixture was stirred at room temperature. The reaction progress was followed by thin-layer chromatography (TLC), and after consumption of starting materials (see Table 1), ethyl acetate (10 mL) was added, and the organic solution was separated from the SiO_2 by filtration. The solvent was evaporated under reduced pressure, and the residue was purified by column chromatography over silica gel (SiO_2), eluting with hexane/ethyl acetate (90:10) and yielding the diastereomers *trans*-**6** and *cis*-**7**, according Table 1.

Method B

The aforementioned whole mixture was previously stirred for 1 min and then irradiated with MW (a domestic Panasonic model Piccolo NN-S42BK, operating at 2.45 MHz) at 548 W[11] for 0.5–1.5 min (Table 1), and the product was extracted and purified according to method A.

Method C

To a mixture of 3-(phenylthio)-citronellal (**2a**, 0.262 g, 1 mmol) and aniline (**3a**, 0.093 g, 1 mmol) in benzene (5 mL), $SiO_2/ZnCl_2$ (10%) (0.120 g) was added at room temperature. The mixture was stirred at room temperature, and the reaction progress was followed by TLC. After

stirring for 6 h (entry 3, Table 1), ethyl acetate (10 mL) was added, and the organic solution was separated from the SiO_2 by filtration. The solvent was evaporated under reduced pressure and the residue was purified according to method A. Spectral data of **6a–i** and **7a–i** are listed. Except when mentioned, the spectral data are related to the major *trans*-isomer **6**, and the relative stereochemistry was assigned only for *trans*-fused OHAs **6** and **6′** (monocrystal x-ray analysis). The minor *trans*-**6′** and *cis*-**7** isomers were characterized by analysis of the ^{1}H NMR spectra of the isomeric mixture and by GC-MS analysis.

Data

(3*S**,4a*R**,9a*S**)-1,2,3,4,4a,9a,10-Octahydro-3,9,9-trimethyl-3-(phenylthio)-acridines, *trans*-**6a** and *cis*-**7a**

cis-**7a** (first eluted fraction): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40–7.44 (m, 2H), 7.19–7.35 (m, 3H), 7.14 (dd, $J = 7.6$ and 1.2 Hz, 1H), 6.99 (td, $J = 7.2$ and 1.6 Hz, 1H), 6.62 (td, $J = 7.6$ and 1.2 Hz, 1H), 6.50 (dd, $J = 8.0$ and 1.2 Hz, 1H), 4.11 (br s, 1H), 3.90–3.93 (m, 1H), 1.50–2.20 (m, 4H), 1.38 (s, 3H), 1.22 (s, 3H), 1.20–1.35 (m, 3H), 1.13 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.2, 137.3, 132.7, 128.5, 128.4, 127.6, 126.6, 125.5, 116.3, 113.6, 47.8, 46.8, 44.7, 44.2, 37.8, 35.4, 32.9, 32.6, 26.0, 19.5. *trans*-**6a** (second eluted fraction): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49–7.52 (m, 2H), 7.32–7.37 (m, 3H), 7.24 (dd, $J = 7.6$ and 1.6 Hz, 1H), 6.95 (td, $J = 7.2$ and 1.6 Hz, 1H), 6.66 (td, $J = 7.2$ and 1.2 Hz, 1H), 6.43 (dd, $J = 7.8$ and 1.2 Hz, 1H), 3.70 (td, $J = 10.8$ and 4.0 Hz, 1H; major diastereomer (3*S**, 4a*R**, 9a*S**)-**6a**), 3.58 (br s, 1H), 3.19 (td, $J = 10.6$ and 4.2 Hz, 1H; minor diastereomer, (3*S**, 4a*S**, 9a*R**)-**6a′**), 1.60–2.00 (m, 4H), 1.35 (s, 3H), 1.26 (s, 3H), 1.25 (s, 3H), 1.30–1.45 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.9, 137.5, 131.7, 131.2, 128.7, 128.6, 126.6, 126.5, 117.2, 113.8, 49.7, 47.6, 46.8, 45.5, 37.8, 34.9, 31.8, 27.4, 26.8, 21.0. MS m/z (rel. int.) 337 ($M^+ - 1$, 52.8), 226 (23.4), 212 (100.0), 77 (27.7). HRMS (ESI): m/z calcd. for $C_{22}H_{28}NS$ $[M + H]^+$: 338.1937; found: 338.1965.

(7a*S**,10*S**,11a*R**)-7,7a,8,9,10,11,11a,12-Octahydro-7,7,10-trimethyl-10-(phenylthio)-benz[*c*]acridines, *trans*-**6b** and *cis*-**7b**

cis-**7b** and *trans*-**6b**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15–7.93 (m, 22H), 5.17 (br s, 1H), 4.11 (br s, 1H), 3.86–3.90 (m, 1H; *cis*-**7b**), 3.77 (td, $J = 11.0$ and 4.4 Hz, 1H; *trans*-**6b**), 1.20–2.40 (m, 14H), 1.40 (s, 3H),

1.38 (s, 3H), 1.32 (s, 3H), 1.29 (s, 3H), 1.26 (s, 3H), 1.11 (s, 3H); (*cis*-**7b** and *trans*-**6b**) ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.4, 137.3, 137.1, 136.7, 132.8, 132.3, 131.7, 128.7, 128.6, 128.5, 128.4, 128.2, 128.0, 125.4, 125.0, 124.8, 124.7, 124.5, 123.4, 122.0, 120.6, 119.7, 117.0, 116.6, 49.8, 47.8, 47.5, 47.2, 46.9, 45.4, 44.7, 43.3, 38.1, 37.7, 35.4, 35.1, 34.0, 32.7, 31.8, 27.3, 27.2, 27.0, 26.6, 21.0, 19.2. *cis*-**7b**: MS *m/z* (rel. int.) 387 ($M^+ - 1$, 100.0), 372 (19.3), 262 (77.1), 194.0 (60.1), 110 (73.9). HRMS (ESI): *m/z* calcd for $C_{26}H_{29}NS$ $[M + H]^+$: 388.2093; found: 388.2125. *trans*-**6b**: MS *m/z* (rel. int.) 387 ($M^+ - 1$, 85.8), 372 (28.6), 262 (36.3), 194.0 (100.0), 110 (72.1). (7a*R**,10*S**,11a*S**)-**6b′**: MS *m/z* (rel. int.) 387 ($M^+ - 1$, 54.5), 262 (41.4), 194.0 (34.5), 110 (100.0).

(3*S**,4a*R**,9a*S**)-1,2,3,4,4a,9a,10-Octahydro-3,7,9,9-tetramethyl-3-(phenylthio)-acridines, *trans*-**6c** and *cis*-**7c**

trans-**6c** (second eluted fraction): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49–7.52 (m, 2H), 7.29–7.36 (m, 3H), 7.04 (d, $J = 1.2$ Hz, 1H), 6.77 (dd, $J = 8.0$ and 1.2 Hz, 1H), 6.37 (d, $J = 8.0$ Hz, 1H), 3.88–3.91 (m, 1H; *cis*-**7c**), 3.66 (td, $J = 10.8$ and 4.0 Hz, 1H; major diastereomer (3*S**,4a*R**,9a*S**)-**6c**), 3.45 (br s, 1H), 3.15 (td, $J = 10.7$ and 4.0 Hz, 1H; minor diastereomer, (3*S**,4a*S**,9a*R**)-**6c′**), 2.23 (s, 3H), 1.60–2.0 (m, 4H), 1.30–1.46 (m, 3H), 1.34 (s, 3H), 1.25 (s, 3H), 1.24 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.6, 137.5, 131.8, 131.3, 128.7, 128.6, 127.9, 127.2, 126.1, 114.0, 49.8, 47.9, 46.9, 45.6, 37.8, 34.9, 31.9, 27.5, 26.9, 21.0, 20.7. MS *m/z* (rel. int.) 351 ($M^+ - 1$, 74.4), 240 (26.7), 226 (100.0), 186.0 (71.8), 77 (21.1). HRMS (ESI): *m/z* calcd. for $C_{23}H_{29}NS$ $[M + H]^+$: 352.2093; found: 352.2115. (3*S**,4a*S**,9a*R**)-**6c′** MS *m/z* (rel. int.) 351 ($M^+ - 1$, 54.1), 240 (17.7), 226 (31.9), 186.0 (100.0), 77 (26.2).

(3*S**,4a*R**,9a*S**)-7-Chloro-1,2,3,4,4a,9a,10-octahydro-3,9,9-trimethyl-3-(phenylthio)-acridines, *trans*-**6d** and *cis*-**7d**

trans-**6d** (second eluted fraction): ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.48–7.50 (m, 2H), 7.32–7.35 (m, 3H), 7.17 (d, $J = 2.4$ Hz, 1H), 6.88 (dd, $J = 8.4$ and 2.4 Hz, 1H), 6.35 (d, $J = 8.4$ Hz, 1H), 3.90 (m, 1H; *cis*-**7d**), 3.67 (td, $J = 10.8$ and 4.0 Hz, 1H; major diastereomer (3*S**,4a*R**,9a*S**)-**6d**), 3.60 (br s, 1H), 3.15 (td, $J = 10.6$ and 4.2 Hz, 1H; minor diastereomer (3*S**,4a*S**,9a*R**)-**6d′**), 1.70–1.93 (m, 4H), 1.33 (s, 3H), 1.25 (s, 3H), 1.22 (s, 3H), 1.30–1.50 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.3, 137.4, 132.7, 131.6, 128.8, 128.6, 126.4, 126.3, 121.4, 114.9, 49.6, 47.1, 46.8, 45.4, 37.6, 35.1, 31.7, 27.1, 26.5, 20.9. MS *m/z* (rel. int.) 371

($M^+ -1$, 48.6), 261 (21.6), 246 (100.0), 206 (67.6), 77 (21.7). HRMS (ESI): m/z calcd. for $C_{22}H_{27}ClNS$ $[M+H]^+$: 372.1547; found: 372.1555. (3*S**,4a*S**,9a*R**)-**6d′** MS m/z (rel. int.) 371 ($M^+ -1$, 38.8), 261 (14.7), 246 (21.7), 206 (100.0), 77 (23.6).

(3*S**,4a*R**,9a*S**)-1,2,3,4,4a,9a,10-Octahydro-3,5,9,9-tetramethyl-3-(phenylthio)-acridines, *trans*-**6e** and *cis*-**7e**

cis-**7e** (first eluted fraction): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43–7.49 (m, 2H), 7.22–7.35 (m, 3H), 7.08 (dd, $J = 7.6$ e 1.2 Hz, 1H), 6.91 (br d, $J = 7.4$ Hz, 1H), 6.62 (t, $J = 7.4$ Hz, 1H), 3.95–4.05 (m, 1H), 3.40 (br s, 1H), 2.20 (s, 3H), 1.36 (s, 3H), 1.26 (s, 3H), 1.12 (s, 3H), 1.20–2.40 (m, 7H). MS m/z (rel. int.) 351 ($M^+ -1$, 77.5), 241 (30.8), 226 (100.0), 186.0 (74.3), 77 (30.3). HRMS (ESI): m/z calcd for $C_{23}H_{29}NS$ $[M+H]^+$: 352.2093; found: 352.2117. *trans*-**6e** (second eluted fraction): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50–7.53 (m, 2H), 7.25–7.36 (m, 3H), 7.16 (dd, $J = 8.0$ and 1.6 Hz, 1H), 6.88 (br d, $J = 7.2$ Hz, 1H), 6.58 (t, $J = 7.6$ Hz, 1H), 3.71 (td, $J = 10.8$ and 4.0 Hz, 1H; major diastereomer **6e**), 3.40 (br s, 1H), 2.07 (s, 3H), 1.38 (s, 3H), 1.27 (s, 3H), 1.24 (s, 3H), 1.20–2.30 (m, 7H); (*cis*-**7e** and *trans*-**6e**) ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.9, 140.4, 137.8, 137.5, 132.5, 131.8, 130.7, 128.8, 128.6, 128.4, 127.7, 127.1, 124.5, 123.5, 120.9, 120.3, 116.4, 115.7, 49.9, 47.9, 47.4, 46.9, 46.8, 45.9, 44.8, 44.2, 37.9, 37.8, 35.4, 35.0, 33.3, 32.5, 31.9, 27.4, 27.0, 26.4, 21.0, 19.4, 17.7, 17.5. MS m/z (rel. int.) 351 ($M^+ -1$, 98.3), 242 (42.3), 226 (39.2), 186.0 (100.0), 77 (30.5). (3*S**,4a*S**,9a*R**)-**6e′** MS m/z (rel. int.) 351 ($M^+ -1$, 53.4), 242 (23.0), 226 (30.0), 186.0 (100.0), 77 (19.7).

(3*S**,4a*R**,9a*S**)-7-Fluoro-1,2,3,4,4a,9a,10-octahydro-3,9,9-trimethyl-3-(phenylthio)-acridines, *trans*-**6f** and *cis*-**7f**

trans-**6f** (second eluted fraction): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48–7.52 (m, 2H), 7.29–7.36 (m, 3H), 6.94 (dd, $J = 10.6$, 2.8 Hz, 1H), 6.66 (ddd, $J = 9.0$, 8.0 and 2.8 Hz, 1H), 3.88–3.90 (m, 1H; *cis*-**7f**), 6.36 (dd, $J = 8.6$ e 5.0 Hz, 1H), 3.65 (td, $J = 10.8$ and 4.4 Hz, 1H; major diastereomer (3*S**,4a*R**,9a*S**)-**6f**), 3.46 (br s, 1H); 3.14 (td, $J = 10.8$ and 4.0 Hz, 1H; minor diastereomer (3*S**,4a*S**,9a*R**)-**6f′**), 1.60–2.00 (m, 4H), 1.28–1.44 (m, 3H), 1.32 (s, 3H), 1.25 (s, 3H), 1.23 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.7 (d, $J_{C\text{-}F} = 233.1$ Hz), 139.1 (d, $J_{C\text{-}F} = 1.4$ Hz), 137.4, 132.6 (d, $J_{C\text{-}F} = 5.6$ Hz), 131.7, 128.7, 128.6, 114.5 (d, $J_{C\text{-}F} = 7.1$ Hz), 113.1 (d, $J_{C\text{-}F} = 22.6$ Hz), 113.0 (d, $J_{C\text{-}F} = 22.6$ Hz), 49.7, 47.3, 46.9, 45.5, 37.7, 35.2,

31.8, 27.3, 26.8, 20.9. MS m/z (rel. int.) 355 ($M^+ -1$, 56.4), 246 (26.0), 230 (100.0), 190.0 (80.5), 77 (18.9). HRMS (ESI): m/z calcd for $C_{22}H_{27}FNS$ $[M+H]^+$: 356.1842; found: 356.1865. (3*S**,4a*S**,9a*R**)-**6f′** MS m/z (rel. int.) 355 ($M^+ -1$, 33.6), 246 (15.7), 230 (21.0), 190.0 (100.0), 77 (11.5). *cis*-**7f** MS m/z (rel. int.) 355 ($M^+ -1$, 65.0), 246 (32.0), 230 (100.0), 190.0 (95.5), 77 (21.8).

(3*S**,4a*R**,9a*S**)-1,2,3,4,4a,9a,10-Octahydro-3-)[(4-methoxyphenyl)thio]-3,7,9,9-tetramethyl-acridines, *trans*-**6g** and *cis*-**7g**

cis-**7g** (first eluted fraction): ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.70–7.50 (m, 5H), 6.96 (d, $J = 1.6$ Hz, 1H), 6.46 (d, $J = 8.0$ Hz, 1H), 4.14 (br s, 1H), 3.88–3.90 (m, 1H), 3.78 (s, 3H), 0.70–2.40 (m, 7H), 2.24 (s, 3H), 1.37 (s, 3H), 1.22 (s, 3H), 1.11 (s, 3H). m/z (rel. int.) 381 ($M^+ -1$, 29.5), 242 (72.6), 186 (65.8), 118 (61.0), 91 (100.0), 77 (45.3). *trans*-**6 g** (second eluted fraction): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (d, $J = 8.4$ Hz, 2H), 7.04 (d, $J = 1.2$ Hz, 1H), 6.85 (d, $J = 8.4$ Hz, 2H), 6.76 (dd, $J = 8.0$ and 1.2 Hz, 1H), 6.37 (d, $J = 8.0$ Hz, 1H), 3.81 (s, 3H), 3.64 (td, $J = 10.6$ and 4.0 Hz, 1H), 3.45 (br s, 1H), 2.23 (s, 3H), 1.15–2.00 (m, 7H), 1.34 (s, 3H), 1.24 (s, 3H), 1.23 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.2, 140.6, 138.8, 131.3, 127.2, 127.1, 126.1, 122.5, 114.1, 114.0, 55.2, 49.4, 47.8, 46.8, 45.4, 37.6, 35.0, 31.8, 27.5, 27.0, 21.0, 20.7. *trans*-**6g**: m/z (rel. int.) 381 ($M^+ -1$, 60.6), 242 (41.7), 186 (100.0), 158 (74.3), 77 (15.2). HRMS (ESI): m/z calcd for $C_{24}H_{31}NOS$ $[M+H]^+$: 382.2199; found: 382.2209. (3*S**,4a*S**,9a*R**)-**6g′**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (d, $J = 8.4$ Hz, 2H), 6.98 (d, $J = 1.2$ Hz, 1H), 6.84 (d, $J = 8.4$ Hz, 2H), 6.72 (dd, $J = 8.0$ and 1.2 Hz, 1H), 6.32 (d, $J = 8.0$ Hz, 1H), 3.80 (s, 3H), 3.45 (br s, 1H), 3.14 (td, $J = 10.4$ and 4.0 Hz, 1H), 2.21 (s, 3H), 1.15–2.00 (m, 7H), 1.31 (s, 3H), 1.27 (s, 3H), 1.08 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.3, 140.4, 139.2, 131.0, 127.2, 127.0, 126.1, 121.8, 114.1, 114.0, 53.4, 48.0, 47.6, 47.4, 46.0, 38.0, 34.7, 27.3, 26.8, 24.4, 21.3, 20.7.

(3*S**,4a*R**,9a*S**)-7-Chloro-1,2,3,4,4a,9a,10-octahydro-3-)[(4-methoxyphenyl)thio]-3,9,9-trimethyl-acridines, *trans*-**6h** and *cis*-**7h**

cis-**7h**, *trans*-**6h** and (3*S**,4a*S**,9a*R**)-**6h′** (*trans*-**6h′**): ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.27–7.43 (m, 2H), 7.06–7.17 (m, 1H), 6.80–6.89 (m, 3H), 6.26–6.42 (m, 1H), 4.11 (m, 1H; *cis*-**7h**), 3.73–3.85 (m, 4), 3.64 (td, $J = 10.9$ and 4.0 Hz, 1H; *trans*-**6h**), 3.11 (td, $J = 10.5$ and 3.8 Hz, 1H; *trans*-**6h′**), 1.0–2.0 (m, 16H), (*cis*-**7h**, *trans*-**6h** and *trans*-**6h′**); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.3, 160.2, 160.0, 141.5, 141.3, 140.8, 139.1,

138.7, 138.6, 132.6, 132.5, 132.3, 129.1, 126.5, 126.3, 123.2, 126.1, 125.3, 123.1, 122.2, 121.6, 121.2, 121.1, 120.3, 114.8, 114.5, 114.4, 114.1, 114.0, 113.9, 55.1, 55.0, 49.2, 47.7, 47.4, 47.3, 47.0, 46.7, 46.6, 46.5, 45.7, 45.1, 43.9, 43.7, 37.9, 37.4, 37.1, 35.5, 35.0, 34.9, 32.3, 32.2, 31.6, 27.0, 26.9, 26.4, 26.3, 25.7, 24.3, 21.1, 20.8, 19.3. *trans*-**6h**: *m/z* (rel. int.) 263 (M^+ $-p$-$CH_3OC_6H_4S$, 0.86), 143 (28.0), 107 (70.0), 93.0 (100.0), 77 (71.5). HRMS (ESI): *m/z* calcd. for $C_{23}H_{28}ClNOS$ $[M + H]^+$: 402.1652; found: 402.1652.

(3*S**,4a*R**,9a*S**)-1,2,3,4,4a,9a,10-Octahydro-3-)
[(4-methoxyphenyl)thio]-3,5,9,9-tetramethyl-acridines, *trans*-**6i** and *cis*-**7i**

cis-**7i** (first eluted fraction): ^1H NMR (400 MHz, $CDCl_3$) δ 7.34 (d, $J = 8.8$ Hz, 2H), 7.06 (d, $J = 6.8$ Hz, 1H), 6.90 (d, $J = 6.4$ Hz, 1H), 6.79 (d, $J = 8.8$ Hz, 2H), 6.58 (t, $J = 7.6$ Hz, 1H), 4.15 (m, 1H), 3.95 (m, 1H), 3.76 (s, 3H), 2.20 (s, 3H), 1.20–1.83 (m, 7H), 1.38 (s, 3H), 1.23 (s, 3H), 1.10 (s, 3H). *m/z* (rel. int.) 381 ($M^+ - 1$, 53.1), 226 (92.2), 186 (100.0), 158 (77.0), 77 (19.0). *trans*-**6i**: ^1H NMR (400 MHz, $CDCl_3$) δ 7.42 (d, $J = 8.8$ Hz, 2H), 7.16 (d, $J = 7.6$ Hz, 1H), 6.81–6.87 (m, 4H), 3.81 (s, 3H), (td, $J = 10.8$ and 4.0 Hz, 1H), 2.07 (s, 3H), 1.20–2.30 (m, 7H), 1.35 (s, 3H), 1.25 (s, 3H), (*cis*-**7i** and *trans*-**6i**); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.1, 140.4, 138.9, 132.6, 127.6, 127.2, 123.5, 123.2, 121.0, 115.7, 114.6, 113.9, 55.2, 47.5, 46.9, 44.7, 43.8, 37.7, 35.4, 33.3, 32.5, 26.4, 19.3, 17.7. *m/z* (rel. int.) 381 ($M^+ - 1$, 68.6), 242 (55.5), 186 (100.0), 158 (67.6), 77 (21.2). HRMS (ESI): *m/z* calcd. for $C_{24}H_{31}NOS$ $[M + H]^+$: 382.2199; found: 382.2206.

General Procedure for the Synthesis of Octahydroacridines 4 and 5

Method A

A mixture of (*R*)-citronellal (**1**, 1.0 mmol) and aniline (**3g**, 1.0 mmol) was added to $SiO_2/ZnCl_2$ (10%) (0.120 g).[10] The mixture was stirred at room temperature, and the reaction progress was followed by TLC. After consumption of the starting materials (see Table 1), ethyl acetate (10 mL) was added, and the organic solution was separated from the SiO_2 by filtration. The solvent was evaporated under reduced pressure, and the residue was purified by column chromatography over silica gel (SiO_2) eluting with hexane/ethyl acetate (90:10), yielding the diastereomers *trans*-**4** and *cis*-**5**, according to Table 1. Spectral data of **4a–b** and **5a–b** are listed below.

Data

7-[(4-Chlorobenzyl)thio]-1,2,3,4,4a,9,9a,10-octahydro-3,9,9-trimethyl-acridines, *trans*-**4a** and *cis*-**5a**

cis-**5a** (first eluted fraction): ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.18–7.23 (m, 2H), 6.86–6.98 (m, 4H), 6.18 (d, $J = 8.4$ Hz, 1H), 3.81 (s, 2H), 3.70–3.73 (m, 1H), 3.71 (br s, 1H), 1.0–1.90 (m, 8H), 1.14 (s, 3H), 1.09 (s, 3H), 0.87 (d, $J = 6.2$ Hz, 3H). *trans*-**4a**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.13–7.16 (m, 2H), 6.17–7.04 (m, 4H), 6.30 (d, $J = 8.2$ Hz, 1H), 3.81 (s, 2H), 3.70 (br s, 1H), 2.98–3.06 (m, 1H), 1.90–2.0 (m, 8H), 1.17 (s, 3H), 0.97 (s, 3H), 0.93 (d, $J = 6.6$ Hz, 3H). (*cis*-**5a** and *trans*-**4a**) ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.3, 143.1, 137.4, 137.3, 135.0, 133.3, 133.1, 132.9, 132.7, 132.3, 132.2, 131.4, 130.3, 130.2, 128.2, 128.1, 119.1, 118.2, 113.9, 113.1, 53.4, 50.5, 46.7, 46.5, 43.9, 43.2, 41.6, 41.5, 40.9, 35.4, 35.0, 34.7, 34.5, 33.5, 30.8, 26.7, 26.2, 25.7, 25.4, 24.5, 22.8, 22.1. HRMS (ESI): m/z calcd. for $C_{23}H_{28}ClNS$ $[M + H]^+$: 385.1631; found: 385.1625.

7-(Dodecylthio)-1,2,3,4,4a,9,9a,10-octahydro-3,9,9-trimethyl-acridines, *trans*-**4b** and *cis*-**5b**

cis-**5b** and *trans*-**4b**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 and 7.31 (2d, $J = 2.0$ Hz, 1H), 7.03 (dd, $J = 8.0$ and 2.0 Hz, 1H), 6.34 and 6.35 (2d, $J = 8.0$ Hz, 1H), 3.81 (m, 1H; *cis*-**5b**), 3.66 (br s, 1H), 1.10–3.00 (m, 1H; *trans*-**4b**), 2.72 (t, $J = 7.2$ Hz, 2H), 0.86–1.88 (m, 40H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.6, 142.5, 131.8, 131.6, 131.5, 131.4, 128.5, 121.0, 120.3, 113.9, 113.2, 50.6, 46.8, 44.2, 43.2, 41.0, 37.0, 36.9, 35.6, 35.0, 34.8, 34.6, 33.9, 31.9, 30.8, 29.7, 29.6, 29.5, 29.4, 29.3, 29.2, 29.1, 28.6, 26.8, 26.4, 26.0, 24.6, 22.9, 22.6, 22.1, 22.0. *trans*-**4b**: m/z (rel. int.) 429 (M^+, 100.0), 414 (15.8), 260 (22.8), 246 (5.0). HRMS (ESI): m/z calcd. for $C_{28}H_{47}NS$ $[M + H]^+$: 430.3508; found: 430.3500.

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