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Stereoselective Syntheses of the Antihistaminic Drug Olopatadine and Its *E*-Isomer

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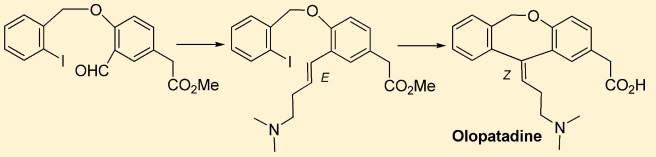
Supporting Information

ABSTRACT: Practical stereoselective synthetic routes to the antihistaminic drug olopatadine and its *E*-isomer have been developed, the key steps being a *trans* stereoselective Wittig olefination using a nonstabilized phosphorus ylide and a stereoselective Heck cyclization. The stereoselectivity of the Wittig reaction depends on both the phosphonium salt anion and the cation present in the base used to generate the ylide.

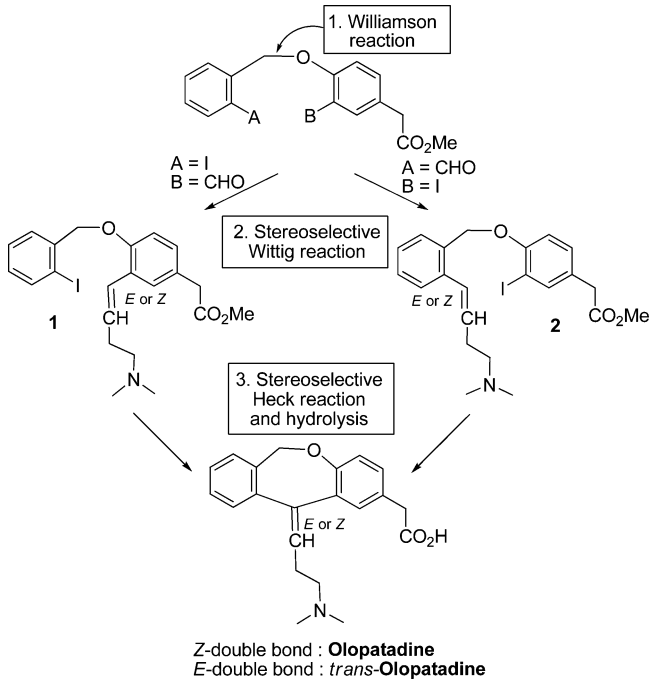


Olopatadine is a nonsedating histamine H1-receptor antagonist with mast cell stabilizing properties. This dual action allows seasonal allergic conjunctivitis and rhinitis signs and symptoms to be controlled.[1] Structurally, olopatadine is a dibenzo[*b*,*e*]oxepin derivative bearing a *Z*-configurated (dimethylamino)propylidene substituent and an acetic acid chain at the C-11 and C-2 positions, respectively, of the tricyclic system. Previous synthetic approaches to olopatadine[2] involve the generation of the trisubstituted exocyclic double bond from a tricyclic dibenz[*b*,*e*]oxepin ketone, which represents a drawback in terms of *Z*/*E* stereoselectivity.[3]

We herein report short and practical stereoselective syntheses of olopatadine and its *E*-isomer (*trans*-olopatadine), based on a common strategy involving successive stereoselective Wittig and intramolecular Heck reactions as the key steps.[4] After a Williamson reaction to assemble the benzyl aryl ether moiety, the Wittig olefination would lead to the key intermediates **1** or **2**, depending on the aromatic aldehyde and aryl iodide derivatives used as the starting materials (Scheme 1). Taking into account that in particular cases, by choosing the appropriate reaction conditions, high selectivity for (*E*)- and/or (*Z*)-alkene can be attained in the Wittig reaction of nonstabilized phosphorus ylides with aldehydes[5] and that the Heck reaction usually involves a *syn*-addition/*syn*-elimination mechanism,[6] the above Williamson−Wittig−Heck strategy could provide stereoselective access to both olopatadine and its *E*-isomer.

The starting aldehyde **5** was prepared from 2-iodobenzyl chloride **3** and 3-formyl-4-hydroxyphenylacetic ester **4**[7] under the reaction conditions indicated in Scheme 2. The Wittig reaction from **5** was initially performed using the ylide generated from the commercially available phosphonium bromide **6** (X = Br) by treatment with KHMDS in toluene (Table 1, entry 1),[8] giving a mixture of *E*/*Z* alkenes in a 1:3 ratio. Similar results were obtained starting from the iodide salt **6** (X = I)[9] (entry 2). Notably, the use of the lithium base

Scheme 1. Synthetic Strategy: A Wittig/Heck Approach to Olopatadine and Its *E*-Isomer



LHMDS to generate the ylide from phosphonium iodide **6** (X = I) produced a dramatic change in the stereoselectivity of the Wittig reaction, leading to a 9:1 *E*/*Z* ratio of alkenes **1** in 73% yield (entry 3).[10] A similar effect, although less pronounced (4:1 *E*/*Z* ratio), was observed from the bromide salt **6** (X = Br) (entry 4). In contrast, the use of phosphonium chloride **6** (X =

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Scheme 2. Wittig Reaction from Aldehyde 5

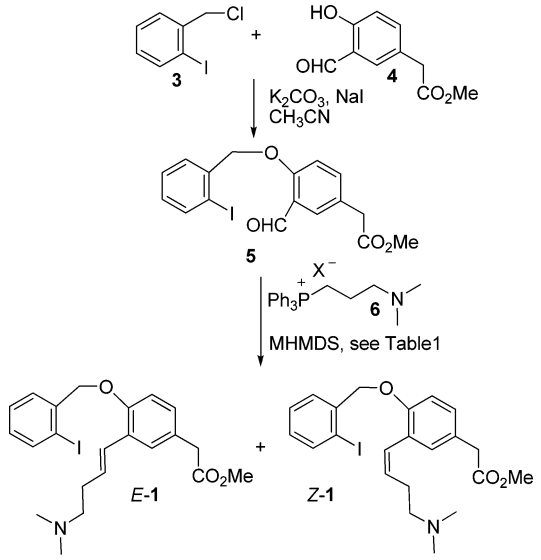

Table 1. Stereochemistry Dependence on the Cation in the Wittig Reaction[a]

entry	base, M	**6**, X	*E*/*Z* ratio[b]	**1**, yield (%)
1	K	Br	1:3	60
2	K	I	1:3	85[c]
3	Li	I	9:1	73
4	Li	Br	4:1	77[c]
5	Li	Cl	1:1.5	37[c]

[a]Reaction conditions: aldehyde **5** (0.02 M in anhydrous toluene), phosphonium salt **6** (4.2 equiv), MHMDS (4.2 equiv), rt. [b]Calculated by ^{1}H NMR and HPLC. [c]Calculated by HPLC from the crude reaction mixture.

Cl)[11] as the ylide precursor gave poor results in terms of both selectivity and chemical yield (entry 5).

The above *trans* selectivity is worthy of comment, as Wittig olefination reactions of nonstabilized phosphorus ylides with aromatic aldehydes usually produce the thermodynamically less stable *cis* isomer as the major product.[5] The presence of a nucleophilic group (for instance, amino) in the side chain of these ylides causes a shift in the stereochemistry of the alkene product toward the *trans* isomer,[12] whose production is also increased by lithium ions.[13]

The pronounced effect of the lithium cation on alkene stereochemistry was also observed in the Wittig reaction from benzaldehyde **9**, which was prepared from 2-formylbenzyl bromide **7**[14] and 4-hydroxy-3-iodophenylacetic ester **8**[15] (Scheme 3). Thus, alkenes **2** were produced in an *E*/*Z* ratio of 1:3 when the ylide was generated in toluene solution from phosphonium iodide **6** (X =I) using KHMDS as the base (Table 2, entry 1). Neither the use of THF as the solvent (entry 2) nor starting from the bromide salt (entry 3) substantially modified the *E*/*Z* ratio. However, when using the lithium base LHMDS to generate the ylide from iodide **6** (X = I), the stereoselectivity was reversed, with a significant enhancement of *E* stereochemistry, leading to an *E*/*Z* ratio of 3.5:1 (entry 4).

From the synthetic standpoint, with four different alkenes now in hand, prepared in acceptable yield and good (*E*-**1**) to acceptable (*Z*-**1**, *E*-**2**, *Z*-**2**) stereoselectivity, we were ready to tackle the key Heck cyclization. The intramolecular Heck

Scheme 3. Wittig Reaction from Aldehyde 9

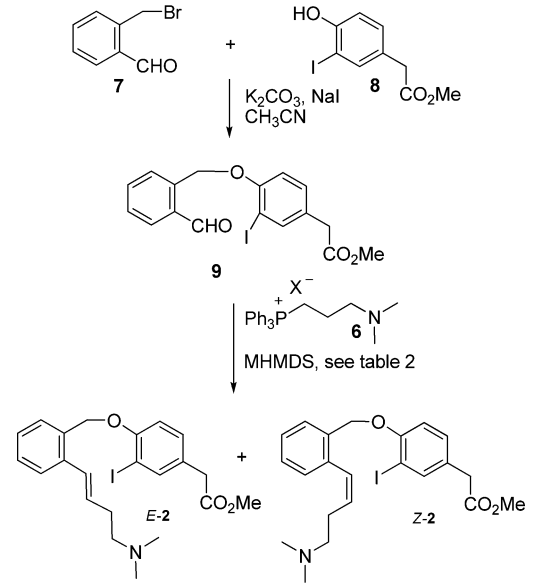

Table 2. Stereochemistry Dependence on the Cation in the Wittig Reaction[a]

entry	base, M	**6**, X	solvent	*E*/*Z* ratio[b]	**2**, yield[c] (%)
1	K	I	toluene	1:3	73
2	K	I	THF	1:4	64
3	K	Br	toluene	1:3	86
4	Li	I	toluene	3.5:1	88

[a]Reaction conditions: aldehyde **9** (0.02 M in anhydrous toluene or THF), phosphonium salt **6** (4.2 equiv), MHMDS (4.2 equiv), rt. [b]Calculated by ^{1}H NMR and HPLC. [c]Calculated by HPLC from the crude reaction mixture.

reaction from iodo alkene *E*-**1** was performed under solid−liquid phase transfer conditions, using a stoichiometric quantity of Bu_4NCl as the transfer agent[16] and K_2CO_3 as the base,[17] in the presence of a catalytic amount of $Pd(OAc)_2$ (without phosphine ligands[18]) in an acetonitrile−water mixture.[19] A single dibenzoxepin derivative **10**, bearing a *Z*-configurated double bond, was formed with complete stereoselectivity in 60% yield.[20] A similar Pd-catalyzed cyclization from iodo alkene *E*-**2** stereoselectively afforded *E* dibenzoxepin **11** in 55% yield. The above results were not unexpected and are consistent with a *syn*-addition of the initially formed arylpalladium intermediate to the alkene, with a subsequent *syn* β-elimination of a hydridopalladium halide, as outlined in Scheme 4.

However, in contrast with the high stereoselectivity observed in the above Heck arylations from *trans* alkenes *E*-**1** and *E*-**2**, the Heck cyclization from *cis* alkenes *Z*-**1** and *Z*-**2** was not stereoselective, leading to mixtures of the cyclized products **10** and **11** (approximate ratios 3:2), probably as a consequence of a competitive Pd(II)-promoted isomerization of the starting *Z*-configurated alkenes to the more stable *E*-isomers.

Finally, alkaline hydrolysis of the cyclized products **10** and **11** furnished the target drug olopatadine and its *E*-isomer, respectively.

In summary, we have developed practical synthetic routes to the antihistaminic drug olopatadine and its *E*-isomer based on a common strategy involving successive highly stereoselective Wittig olefination and Heck cyclization reactions as the key steps.

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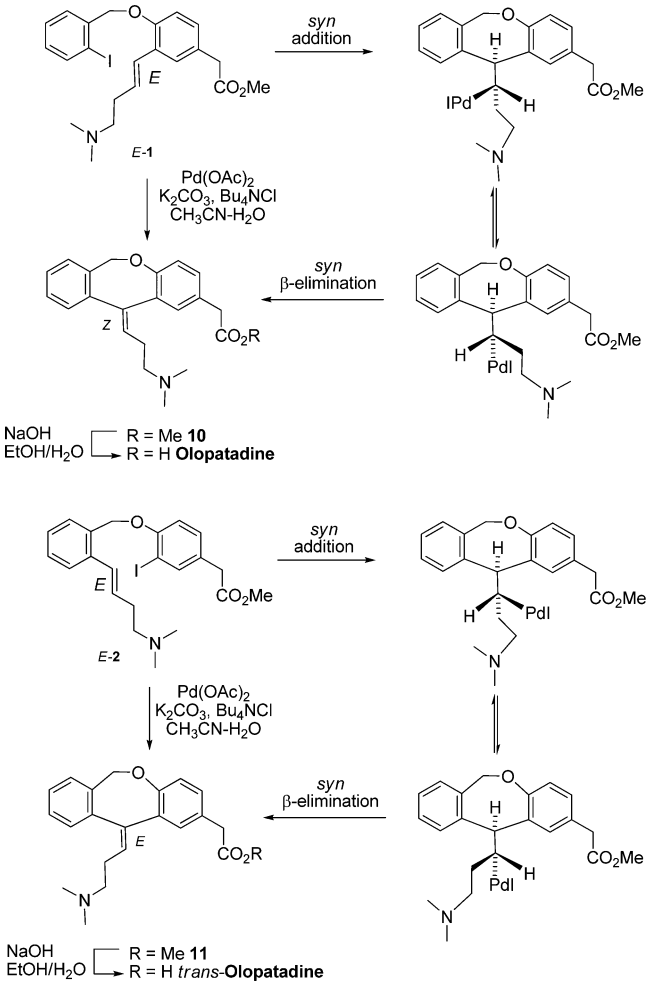
Scheme 4. Stereoselective Heck Reactions



EXPERIMENTAL SECTION

(3-Dimethylaminopropyl)triphenylphosphonium Iodide (6, X = I). A mixture of 3-(dimethylamino)-1-propyl chloride hydrochloride (20 g, 126 mmol), PPh_3 (33 g, 126 mmol), and NaI (19 g, 126 mol) in acetonitrile (80 mL) was heated at reflux for 5.5 days. After cooling at rt, H_2O–acetonitrile (2:1, 360 mL) was added, and the mixture was stirred at 45 °C for 0.5 h. The resulting suspension was filtered, solid K_2CO_3 was added to the filtrate until pH 9–10, and the solution was extracted with CH_2Cl_2 (3 × 150 mL). The combined organic extracts were dried and concentrated, and the resulting oil was dissolved in CH_2Cl_2 (25 mL). AcOEt (120 mL) was added, and the mixture was stirred until the formation of a white solid, which was collected by filtration (52 g, 87%): mp 138–141 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.75–1.87 (m, 2H), 2.13 (s, 6H), 2.54 (t, J = 5.9 Hz, 2H), 3.65–3.75 (m, 2H), 7.70–7.87 (m, 15H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 20.4 (d, J = 52.2 Hz), 20.5 (d, J = 3.3 Hz), 45.2 (s), 58.2 (d, J = 16.0 Hz), 117.9 (d, J = 86.2 Hz), 130.3 (d, J = 12.6 Hz), 133.3 (d, J = 10.5 Hz), 134.9 (d, J = 2.7 Hz); IR (KBr) 995, 1111, 1438 cm^{-1}. Anal. Calcd for $C_{23}H_{27}NIP$: C, 58.11; H, 5.73; N, 2.95; I, 26.70. Found: C, 58.13; H, 5.66; N, 2.90; I, 26.58.

(3-Dimethylaminopropyl)triphenylphosphonium Chloride (6, X = Cl). A mixture of 3-(dimethylamino)-1-propyl chloride hydrochloride (10 g, 63 mmol) and PPh_3 (16.5 g, 63 mmol) in 1-butanol (40 mL) was heated at reflux for 4 days. The mixture was cooled at rt, toluene–Et_2O (1:1, 50 mL) was added, and the solution was kept in the refrigerator for a night. The solid formed was filtered and washed with toluene–Et_2O and Et_2O to give pure **6**·HCl (X = Cl) (15.6 g, 59%) as a white powder. A solution of this hydrochloride in 2 N aqueous K_2CO_3 (50 mL) was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic extracts were dried and concentrated to give an oil, which was cooled in the refrigerator for 2 days to afford **6**, (X =Cl) as a hygroscopic white solid (12.4 g, 90%): mp 188–191 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.74–1.87 (m, 2H), 2.12 (s, 6H), 2.53 (t, J = 6.0 Hz, 2H), 3.77–3.89 (m, 2H), 7.69–7.89 (m, 15H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 19.9 (d, J = 52.2 Hz), 20.5 (d, J = 3.3 Hz), 45.0 (s), 58.2 (d, J = 16.0 Hz), 118.0 (d, J = 86.2 Hz), 130.2 (d, J = 12.6 Hz), 133.2 (d, J = 9.9 Hz), 134.7 (d, J = 2.8 Hz); IR (KBr) 995, 1112, 1434 cm^{-1}. Anal. Calcd for $C_{23}H_{27}NClP$: C, 71.96; H, 7.09; N, 3.65; Cl, 9.24. Found: C, 71.93; H, 7.15; N, 3.52; Cl, 9.45.

Methyl [3-Formyl-4-(2-iodobenzyloxy)phenyl]acetate (5). A solution of methyl (3-formyl-4-hydroxyphenyl)acetate (16.7 g, 85.9 mmol) in acetonitrile (68 mL) was slowly added at rt to a mixture of 1-(chloromethyl)-2-iodobenzene (21.7 g, 85.9 mmol), K_2CO_3 (13.1 g, 94.5 mmol), and NaI (3.22 g, 21.5 mmol) in acetonitrile (273 mL), and the mixture was heated at reflux for 3 h. The solid was separated by filtration, and the filtrate was concentrated. The resulting residue was dissolved in toluene (330 mL), and the organic solution was washed with 0.1 N aqueous NaOH and H_2O, dried, and concentrated. The residue was dissolved in acetone (330 mL) and poured into H_2O (500 mL). The mixture was filtered, and the resulting solid was crystallized from toluene–cyclohexane to afford **5** (24.7 g, 70%): mp 68–70 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.61 (s, 2H), 3.70 (s, 3H), 5.15 (s, 2H), 7.00–7.10 (m, 2H), 7.37–7.42 (m, 1H), 7.48–7.51 (m, 2H), 7.77 (d, J = 2.1 Hz, 1H), 7.90 (dd, J = 7.8, 1.2 Hz, 1H), 10.55 (s, 1H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 39.9 (CH_2), 52.1 (CH_3), 74.4 (CH_2), 97.2 (C), 113.3 (CH), 124.9 (C), 126.9 (C), 128.4 (CH), 128.6 (CH), 129.2 (CH), 129.8 (CH), 136.6 (CH), 138.0 (C), 139.4 (CH), 159.6 (C), 171.5 (C), 189.2 (CH); IR (NaCl) 1158, 1249, 1683, 1736, 2700, 2900 cm^{-1}. Anal. Calcd for $C_{17}H_{15}IO_4$: C, 49.78; H, 3.69. Found: C, 49.67; H, 3.66.

Methyl [4-(2-Formylbenzyloxy)-3-iodophenyl]acetate (9). Operating as above, from 2-(bromomethyl)benzaldehyde (11 g, 55.3 mmol), methyl (4-hydroxy-3-iodophenyl)acetate (16.1 g, 55 mmol), K_2CO_3 (8.36 g, 60.5 mmol), and NaI (2.07 g, 13.8 mmol) in acetonitrile (220 mL), compound **9** (18 g, 80%) was obtained after crystallization from acetone–H_2O: mp 93–97 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.54 (s, 2H), 3.70 (s, 3H), 5.55 (s, 2H), 6.90 (d, J = 8.4 Hz, 1H), 7.46 (dd, J = 8.2, 2.2 Hz, 1H), 7.54 (dd, J = 7.8, 7.5 Hz, 1H), 7.67–7.74 (m, 2H), 7.88 (dd, J = 6.0, 1.3 Hz, 1H), 8.08 (d, J = 7.8 Hz, 1H), 10.15 (s, 1H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 39.6 (CH_2), 52.1 (CH_3), 68.6 (CH_2), 86.4 (C), 112.3 (CH), 127.4 (CH), 127.7 (CH), 128.4 (C), 130.4 (CH), 132.4 (C), 134.2 (CH), 134.5 (CH), 138.8 (C), 140.0 (CH), 156.0 (C), 171.6 (C), 193.4 (CH); IR (KBr) 1252, 1691, 1731, 2750, 2833 cm^{-1}. Anal. Calcd for $C_{17}H_{15}IO_4$: C, 49.78; H, 3.69; I, 30.94. Found: C, 49.81; H, 3.53; I, 31.24.

Methyl 3-[4-(Dimethylamino)but-1-enyl]-4-(2-iodobenzyloxy)phenylacetate (1). LHMDS (1 M in THF, 51.5 mL, 51.5 mmol) was added dropwise to a suspension of **6** (X = I) (24.3, 51.2 mmol) in anhydrous toluene (300 mL), and the resulting mixture was stirred at rt for 1 h. A solution of **5** (5.00 g, 12.2 mmol) in anhydrous toluene (170 mL) was added, and the resulting mixture was stirred at rt for 2.5 h. The reaction was quenched with H_2O (150 mL), and the aqueous layer was extracted with toluene. The combined organic extracts were extracted with 2 N aqueous HCl (150 mL), and then solid K_2CO_3 was added to the aqueous phase until pH 9. The alkaline solution was extracted with EtOAc, and the extracts were dried and concentrated. Column chromatography (Al_2O_3, hexane–EtOAc 95:5 to 75:25) afforded compound **1** (4.26 g, 73%; E/Z 9:1) as an oil. Pure samples of both isomers were obtained after additional column chromatography.

Data for E-**1**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.27 (s, 6H), 2.39–2.45 (m, 4H), 3.55 (s, 2H), 3.68 (s, 3H), 5.04 (s, 2H), 6.18–6.29 (m, 1H), 6.81 (d, J = 8.7 Hz, 1H), 6.84 (d, J = 16.2 Hz, 1H), 6.99–7.09 (m, 2H), 7.34–7.39 (m, 2H), 7.50 (dd, J = 7.5, 1.8 Hz, 1H), 7.86 (dd, J = 7.9, 1.2 Hz, 1H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 31.8 (CH_2); 40.4 (CH_2), 45.4 ($2CH_3$); 52.0 (CH_3), 59.4 (CH_2), 74.4 (CH_2), 96.9 (C), 112.8 (CH), 125.1 (CH), 126.6 (C), 127.2 (C), 127.3 (CH), 128.3 (CH), 128.4 (CH), 128.6 (CH), 129.3 (CH), 129.4 (CH), 139.1 (CH), 139.2 (C), 154.1 (C), 172.2 (C); IR (NaCl) 1245, 1737

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cm^{-1}. Anal. Calcd for $C_{22}H_{26}NIO_3$: C, 55.12; H, 5.47; N, 2.92. Found: C, 55.12; H, 5.48; N, 2.83.

Data for *Z*-**1**: ^1H NMR (300 MHz, $CDCl_3$) δ 2.22 (s, 6H), 2.36−2.51 (m, 4H), 3.57 (s, 2H), 3.68 (s, 3H), 5.02 (s, 2H), 5.74 (dt, J = 11.4, 6.8 Hz, 1H), 6.67 (d, J = 11.4 Hz, 1H); 6.84 (d, J = 8.7 Hz, 1H), 6.97−7.13 (m, 2H), 7.20 (d, J = 1.8 Hz, 1H), 7.32−7.40 (m, 1H), 7.48−7.51 (m, 1H), 7.84 (dd, J = 7.8, 1.2 Hz, 1H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 27.1 (CH_2), 40.4 (CH_2), 45.3 ($2CH_3$), 52.0 (CH_3), 59.4 (CH_2), 74.2 (CH_2), 96.7 (C), 112.3 (CH), 125.2 (CH), 126.0 (C), 127.0 (C), 128.3 (2CH), 128.7 (CH), 129.3 (CH), 130.4 (CH), 130.9 (CH), 139.0 (CH), 139.2 (C), 154.9 (C), 172.1 (C); IR (NaCl) 1244, 1738 cm^{-1}. Anal. Calcd for $C_{22}H_{26}NIO_3$: C, 55.12; H, 5.47; N, 2.92. Found: C, 55.17; H, 5.54; N, 2.87.

Methyl 4-{2-[4-(Dimethylamino)but-1-enyl]benzyloxy}-3-iodophenylacetate (2). Operating as above, from aldehyde **9**, under the reaction conditions of Table 2, mixtures of *E*-**2** and *Z*-**2** were obtained. Column chromatography (Al_2O_3, hexane−EtOAc 95:5 to 75:25) afforded the pure isomers as oils.

Data for *E*-**2**: ^1H NMR (300 MHz, $CDCl_3$) δ 2.27 (s, 6H), 2.41−2.44 (m, 4H), 3.52 (s, 2H), 3.69 (s, 3H), 5.14 (s, 2H), 6.08−6.19 (m, 1H), 6.72 (d, J = 15.6 Hz, 1H), 6.83 (d, J = 8.4 Hz, 1H), 7.18−7.31 (m, 3H), 7.46−7.53 (m, 2H), 7.71 (d, J = 2.1 Hz, 1H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 31.8 (CH_2), 39.6 (CH_2), 45.5 ($2CH_3$), 52.1 (CH_3), 59.3 (CH_2), 69.4 (CH_2), 86.7 (C), 112.5 (CH), 126.1 (CH), 127.0 (CH), 127.5 (CH), 128.2 (CH), 128.2 (C), 128.4 (CH), 130.2 (CH), 131.5 (CH), 132.6 (C), 136.6 (C), 140.1 (CH), 156.3 (C), 171.7 (C); IR (NaCl) 1249, 1488, 1738 cm^{-1}. Anal. Calcd for $C_{22}H_{26}NIO_3$: C, 55.12; H, 5.47; I, 26.47; N, 2.92. Found: C, 54.97; H, 5.43; I, 26.63; N, 2.85.

Data for *Z*-**2**: ^1H NMR (300 MHz, $CDCl_3$) δ 2.17 (s, 6H), 2.29−2.35 (m, 4H), 3.51 (s, 2H), 3.68 (s, 3H), 5.05 (s, 2H), 5.76−5.85 (m, 1H), 6.60 (d, J = 11.40 Hz, 1H), 6.78 (d, J = 8.1 Hz, 1H), 7.16−7.31 (m, 4H), 7.63−7.66 (m, 1H), 7.70 (d, J = 2.4 Hz, 1H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 26.9 (CH_2), 39.6 (CH_2), 45.3 ($2CH_3$), 52.0 (CH_3), 59.3 (CH_2), 68.9 (CH_2), 86.6 (C), 112.2 (CH), 127.1 (CH), 127.4 (2CH), 127.5 (CH), 128.1 (C), 129.1 (CH), 130.1 (CH), 131.8 (CH), 134.0 (C), 135.6 (C), 140.0 (CH), 156.3 (C), 171.6 (C); IR (NaCl) 1250, 1489, 1738 cm^{-1}. Anal. Calcd for $C_{22}H_{26}NIO_3$: C, 55.12; H, 5.47; I, 26.47; N, 2.92. Found: C, 55.21; H, 5.68; I, 25.16; N, 2.87.

(*Z*)-Methyl 11-[3-(Dimethylamino)propylidene]-6,11-dihydrodibenz[*b*,*e*]oxepin-2-acetate (10). A mixture of the compound of *E*-**1** (600 mg, 1.25 mmol), K_2CO_3 (436 mg, 3.15 mmol), and Bu_4NCl (349 mg, 1.25 mmol) in 10:1 acetonitrile−H_2O (24 mL) was stirred at rt for 15 min, $Pd(OAc)_2$ (57 mg, 0.25 mmol) was added, and the mixture was stirred at 60 °C for 24 h. The solvent was removed under reduced pressure, and the resulting residue was dissolved in EtOAc (40 mL) and washed with saturated aqueous $NaHCO_3$ and aqueous NaCl solutions. The organic phase was dried, filtered, and concentrated. Column chromatography (Al_2O_3, hexane−EtOAc 95:5 to 75:25) of the residue afforded **10** (264 mg, 60%) as an oil: ^1H NMR (300 MHz, $CDCl_3$) δ 2.22 (s, 6H), 2.41−2.46 (m, 2H), 2.56−2.63 (m, 2H), 3.52 (s, 2H), 3.66 (s, 3H), 5.18 (br, 2H), 5.71 (t, J = 7.2 Hz, 1H), 6.80 (d, J = 8.4 Hz, 1H), 7.02−7.09 (m, 2H), 7.22−7.30 (m, 4H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 28.0 (CH_2), 40.2 (CH_2), 45.4 ($2CH_3$), 51.9 (CH_3), 59.4 (CH_2), 70.3 (CH_2), 119.6 (CH), 123.8 (C), 125.5 (C), 126.1 (CH), 127.3 (2CH), 128.9 (CH), 129.8 (CH), 130.7 (CH), 131.9 (CH), 133.5 (C), 139.5 (C), 145.5 (C), 154.4 (C), 172.0 (C); IR (NaCl) 1225, 1489, 1739 cm^{-1}. Anal. Calcd for $C_{22}H_{25}NO_3 \cdot 1/4H_2O$: C, 74.24; H, 7.22; N, 3.94. Found: C, 74.59; H, 7.14; N, 3.77.

(*E*)-Methyl 11-[3-(Dimethylamino)propylidene]-6,11-dihydrodibenz[*b*,*e*]oxepin-2-acetate (11). Operating as in the above preparation of **10**, from *E*-**2** (100 mg, 0.21 mmol), compound **11** (40 mg, 55%) was obtained as an oil after column chromatography (Al_2O_3, hexane−EtOAc 95:5 to 75:25): ^1H NMR (300 MHz, $CDCl_3$) δ 2.16 (s, 6H), 2.28−2.43 (m, 4H), 3.53 (s, 2H), 3.67 (s, 3H), 4.78 (br, 1H), 5.54 (br, 1H), 6.03 (t, J = 6.9 Hz, 1H), 6.70 (d, J = 8.4 Hz, 1H), 7.20 (dd, J = 8.5, 2.2 Hz, 1H), 7.17−7.37 (m, 5H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 27.7 (CH_2), 40.2 (CH_2), 45.3 ($2CH_3$), 52.0 (CH_3), 59.2 (CH_2), 70.0 (CH_2), 119.3 (CH), 126.1 (C), 127.2 (C), 127.7 (CH), 127.8 (CH), 128.1 (CH), 128.4 (CH), 129.6 (CH), 130.2 (CH), 130.7 (CH), 134.1 (C), 139.6 (C), 141.0 (C), 154.1 (C), 172.2 (C); IR (NaCl) 1224, 1489, 1738 cm^{-1}. Anal. Calcd for $C_{22}H_{25}NO_3$: C, 75.19; H, 7.17; N, 3.99. Found: C, 74.82; H, 7.14; N, 3.81.

(*Z*)-11-[3-(Dimethylamino)propylidene]-6,11-dihydrodibenz[*b*,*e*]oxepin-2-acetic Acid Hydrochloride. 5 N aqueous NaOH (6.2 mL, 31.0 mmol) was added to a solution of **10** (3.32 g, 9.45 mmol) in MeOH (105 mL) and H_2O (21 mL). The mixture was stirred at rt for 3 h, neutralized with 2 N aqueous HCl, and concentrated to dryness. The resulting residue was dissolved in H_2O, and the solution was filtered through an ionic exchange resin DIAION HP-20 (H_2O until negative test of $AgNO_3$ and then MeOH as eluents). The methanolic fractions gave olopatadine (2.64 g, 83%). 37% HCl (1 mL, 12.0 mmol) was added to a stirred solution of the above olopatadine in THF (65 mL), and the mixture was stirred for 5 min. The solid formed was filtered and suspended in acetone (60 mL). The suspension was refluxed for 30 min, cooled, and filtered to give olopatadine hydrochloride as a solid (2.33 g, 66% overall): mp 231−233 °C (dec); ^1H NMR (300 MHz, CD_3OD) δ 2.86 (s, 6H), 2.83−2.91 (m, 2H), 3.28−3.34 (m, 2H), 3.57 (s, 2H), 5.19 (br, 2H), 5.67 (t, J = 7.3 Hz, 1H), 6.81 (d, J = 8.4 Hz, 1H), 7.07−7.13 (m, 2H), 7.26−7.37 (m, 4H); ^{13}C NMR (75.4 MHz, CD_3OD) δ 26.4 (CH_2), 40.5 (CH_2), 43.4 ($2CH_3$), 58.0 (CH_2), 71.5 (CH_2), 120.3 (CH), 124.8 (C), 126.5 (CH), 127.0 (CH), 128.4 (C), 128.5 (CH), 129.0 (CH), 130.1 (CH), 131.7 (CH), 132.8 (CH), 135.1 (C), 144.5 (C), 145.6 (C), 155.9 (C), 175.7 (C); IR (KBr) 1225, 1491, 1716, 2927 cm^{-1}. Anal. Calcd for $C_{21}H_{24}NClO_3 \cdot H_2O$: C, 64.36; H, 6.69; N, 3.57. Found: C, 64.59; H, 6.30; N, 3.63.

(*E*)-11-[3-(Dimethylamino)propylidene]-6,11-dihydrodibenz[*b*,*e*]oxepin-2-acetic Acid Hydrochloride. Operating as above, from ester **11** (973 mg, 2.77 mmol), *trans*-olopatadine hydrochloride was obtained as a white solid (728 mg, 70%): mp 170−173 °C; ^1H NMR (300 MHz, CD_3OD) δ 2.56−2.63 (m, 2H), 2.75 (s, 6H), 3.13 (t, J = 7.6 Hz, 2H), 3.53 (s, 2H), 4.78 (br, 1H), 5.51 (br, 1H), 5.98 (t, J = 7.2 Hz, 1H), 6.69 (d, J = 8.4 Hz, 1H), 7.06 (dd, J = 8.3, 2.3 Hz, 1H), 7.25−7.44 (m, 5H); ^{13}C NMR (75.4 MHz, CD_3OD) δ 26.0 (CH_2), 40.8 (CH_2), 43.3 ($2CH_3$), 57.9 (CH_2), 70.9 (CH_2), 120.3 (CH), 125.9 (CH), 127.6 (C), 128.5 (C), 128.6 (CH), 129.5 (2CH), 130.0 (CH), 131.5 (CH), 132.0 (CH), 135.8 (C), 141.3 (C), 144.2 (C), 155.6 (C), 175.7 (C); IR (KBr) 1223, 1484, 1725, 2960 cm^{-1}. Anal. Calcd for $C_{21}H_{24}NClO_3 \cdot H_2O$: C, 64.36; H, 6.69; N, 3.57. Found: C, 64.66; H, 6.47; N, 3.56.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Copies of the ^1H and ^{13}C NMR spectra of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ DEDICATION

Dedicated to Prof. Miguel A. Miranda on the occasion of his 60th birthday.

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