Application of a Cross-Metathesis and Intramolecular Aza-Diels–Alder Sequence to the Synthesis of *trans*-2,3-Disubstituted Tetrahydroquinolines

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Abstract: The synthesis of 2,3-disubstituted tetrahydroquinolines has been achieved by first performing a cross-metathesis of different alkenes with readily available *N*-allyloxycarbonyl-2-chloromethylaniline. Among the catalysts tested, Hoveyda–Grubbs reagent appeared to be the most suitable, reaching the substituted analogues with complete *E*-stereocontrol and convenient yields. An intramolecular aza-Diels–Alder reaction was further carried out in the presence of potassium phosphate as promoter to deliver the corresponding 2,3-disubstituted tetrahydroquinolines.

Key words: cross-metathesis, azaxylylenes, cycloadditions, Diels–Alder reaction

The tetrahydroquinoline heterocycle is a very important subunit that is found in a large number of biologically active compounds with a large range of activities.[1,2] Galipinine (**1**; Figure 1), for example, has been isolated from *Galipea officinalis* trunk bark and exhibits activity against *plasmodium falciparum*, the protozoan parasite responsible of malaria;[3] the synthetic compound **2**, known as SL 25.1131, is a reversible monoamine oxidase that is structurally related to befloxatone and has shown real therapeutic potential in the early phase of treatment against Parkinson's disease.[4] Virantmycin (**3**), an antiviral agent, also possesses a highly functionalized tetrahydroquinoline ring.[5]

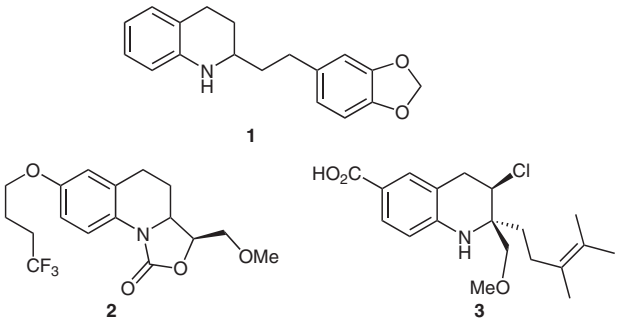
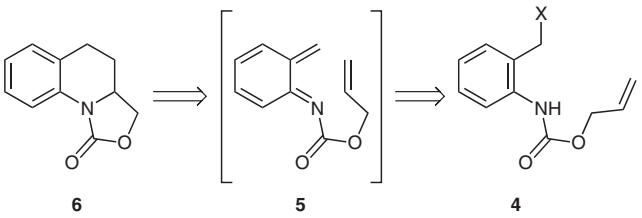


Figure 1 Naturally occurring tetrahydroquinolines

To date, numerous methods have been reported to access these heterocycles.[6,7] Among them, selective reduction of quinolines seems the most straightforward approach, however, this route does not meet the criteria of supplying diversity in organic chemistry.[8] Aza-Diels–Alder reactions also seem a very attractive way to build the heterocycle moiety.[9] As pericyclic reactions, high level of stereocontrol should also be expected. Furthermore, the acyclic precursors could be prepared from readily available compounds as already pointed out in previous studies. Ferraccioli et al. reported the thermal decomposition of benzoxazin-2-one to generate aza-orthoxylylene, which further reacted in either an inter- or intramolecular manner with dienophiles.[10] The latter strategy was considered for the total synthesis of **3** by Steinhagen and Corey[11] and, more recently, by Bräse et al.[12] The Bräse group studied in detail the reaction of **4** under thermal conditions and developed an efficient route to the tricyclic oxazolidinone **6** (Scheme 1).[13] Finally, it should be mentioned that a photochemical activation based on a sigmatropic hydrogen shift was recently reported by Kutateladze et al. from parent benzaldehyde structures.[14]



Scheme 1 Access to tetrahydroquinolines by aza-Diels–Alder reaction

Cross-metathesis is a very useful process for the synthesis of 1,2-disubstituted alkenes when performed with two terminal olefins.[15] Thanks to the discovery of powerful catalysts such as Grubbs type II (GB_{II}) and Hoveyda–Grubbs (HG) catalysts (Figure 2), which tolerate numerous functionalities, this reaction has been applied to the synthesis of complex structures and natural products albeit far less often than the related ring closure.[16,17]

Control of the *E*/*Z* selectivity in cross-metathesis has remained a problem until recently. In the presence of the catalysts mentioned above, formation of the thermodynamically preferred isomer – usually *E* – is observed. Interestingly, the recent design of efficient catalysts by Hoveyda and colleagues and Grubbs and co-workers allows formation of the *Z*-isomer.[18,19] In connection with our interest in metathesis processes and their direct applications in total synthesis,[20] we have investigated a two-

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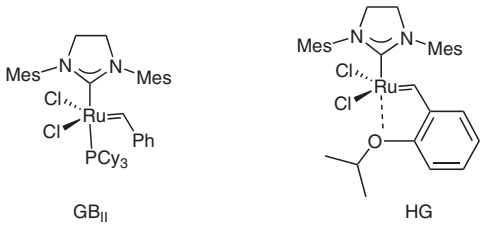
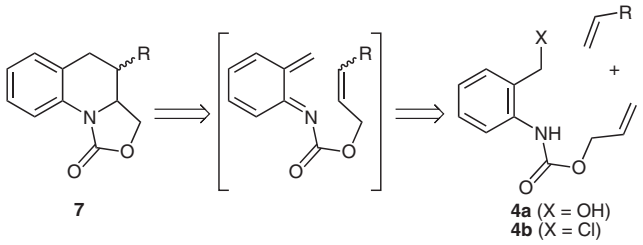


Figure 2 Ruthenium-based catalysts used for this study

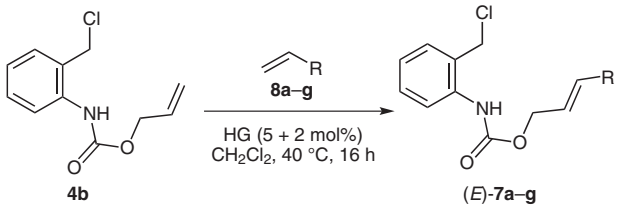
step approach to the synthesis of 2,3-disubstituted tetrahydroquinolines by a thermal [4+2] cycloaddition from related substituted carbamates. To readily prepare these structures, it was anticipated that a cross-metathesis from compounds **4a** and **4b** and various alkenes could allow the expected functionalization of the olefinic moiety to be introduced before the cycloaddition step (Scheme 2).



Scheme 2 Strategy adopted for the synthesis of 2,3-tetrahydroquinolines

Compound **4a** (X = OH), which was easily prepared from commercially available *o*-amino benzyl alcohol and allyl chloroformate,[13] was first tested for cross-metatheses. However, in the presence of GB_{II} or HG catalyst, only low conversion was observed even after a long reaction time.

Table 1 Cross-Metathesis of **4b** with Alkenes **8a–g**

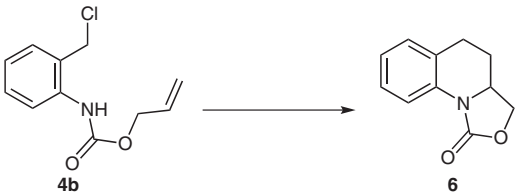


8	R	Conv. (%)	7	Yield (%)[a]
8a	Ph	65	**7a**	37
8b	*p*-$F_3CC_6H_4$	74	**7b**	32
8c	*m*-$F_3CC_6H_4$	100	**7c**	63
8d	*n*-Bu	77	**7d**	49
8e	*n*-Hex	84	**7e**	62
8f	Ac	100	**7f**	80
8g	*p*-MeC_6H_4CO	95	**7g**	71

[a] Isolated yield.

In contrast, when the same reaction was conducted with chloro-derivative **4b** and catalyzed with HG[16b] the expected adducts were furnished in reasonable yields and reaction times with complete *E*-selectivity in all cases (Table 1). Concerning the [4+2] cycloaddition step, previous studies had revealed that use of cesium carbonate as the base could promote the formation of the tricyclic tetrahydroquinoline **6** from **4b**.[12] In order to find a less expensive and less hygroscopic reagent and also to decrease the reaction time, we examined new conditions using the same unsubstituted starting material; the results are reported in Table 2.

Table 2 Optimization of the Synthesis of **6** from **4b**



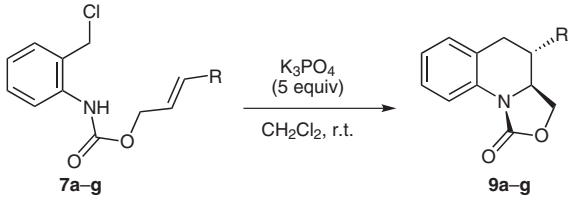
Base	Equiv	Solvent	Temp (°C)	Time (d)	Yield (%)
Cs_2CO_3	3	CH_2Cl_2	23	3	70
Cs_2CO_3	3	DCE	80	16 h	86
guanidine	3	CH_2Cl_2	23	3	0
KF, Al_2O_3	3	CH_2Cl_2	23	3	–[a]
K_3PO_4	3	CH_2Cl_2	23	7	88
K_3PO_4	5	CH_2Cl_2	23	3	82
K_3PO_4	5	CH_2Cl_2	110[b]	2 h	89

[a] Degradation of the starting material.
[b] Reaction performed under microwave activation.

As previously reported, reactions promoted by cesium carbonate delivered compound **6** in high yields. When the reaction was performed in dichloromethane at room temperature for three days in the presence of potassium triphosphate, compound **6** was isolated with a similar chemical yield. This value was slightly improved to 89% under microwave activation, indeed the reaction time was significantly reduced to only two hours. Classic thermal activation and microwave-assisted reactions were applied to compounds **7a–g** (Table 3). The cycloaddition proceeded efficiently with aryl derivatives (Table 3, entries 1–5). In all cases, a single stereoisomer was isolated, for which a *trans* relationship was assigned and confirmed by NOE measurements. In comparison with previous attempts at the synthesis of **6**, microwave activation applied to **7c** gave lower yields.

In contrast, substrates **7d** and **7e**, possessing an alkyl moiety, furnished the expected tetrahydroquinolines in very low yields with formation of a large number of side products being observed by TLC analysis.

Table 3 Intramolecular Thermal Cycloadditions of Esters **7a–g**

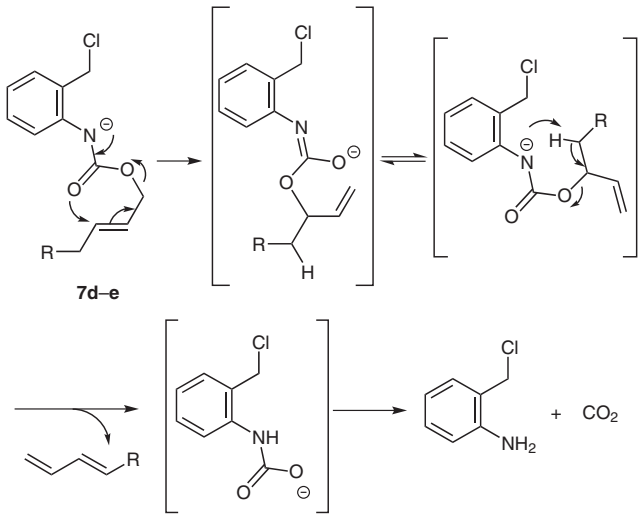


7a–g **9a–g**

Entry	7	R	Temp (°C)	Time (d)	9 (%)[a]
1	**7a**	Ph	23	7	56
2	**7a**	Ph	23	3	51[b]
3	**7b**	*p*-$F_3CC_6H_4$	23	7	45
4	**7c**	*m*-$F_3CC_6H_4$	23	7	66
5	**7c**	*m*-$F_3CC_6H_4$	100	2 h	54[c]
6	**7d**	*n*-Bu	23	7	11
7	**7e**	*n*-Hex	23	7	8
8	**7f**	Ac	23	7	71
9	**7g**	*p*-MeC_6H_4CO	23	7	62

[a] Isolated yield.
[b] Reaction performed with Cs_2CO_3 as base.
[c] Reaction performed under microwave activation.

We assumed that under continuous heating and basic conditions, these substrates underwent a hydrogen atom abstraction leading, after allylic rearrangement and β-elimination, to cleavage of the carbamate moiety (Scheme 3). Interestingly, compounds (*E*)-**7f** and (*E*)-**7g**, bearing an electron-withdrawing group, were smoothly converted into the tricyclic ketones **9f** and **9g**, respectively, in high yields.



Scheme 3 Competitive allylic rearrangement and β-elimination

In conclusion, we have reported the synthesis of 3-substituted oxazolidinotetrahydroquinolines by merging a cross-metathesis and an intramolecular aza-Diels–Alder reaction. Best results were obtained by using Hoveyda–Grubbs catalyst for the first step, whereas inexpensive and non-hygroscopic potassium phosphate was used as base for the generation of the azaxylylene intermediate.

All commercially available compounds were used without further purification. Solvents were dried according to standard procedures. Petroleum ether (PE) refers to a hydrocarbon mixture with a boiling range of 40–60 °C. Column chromatography was performed with silica gel (0.040–0.063 mm, ROTH). NMR spectra were recorded at 293 K, using a 300 MHz spectrometer (Bruker, AMX 300); shifts are referenced relative to deuterated solvent residual peaks. High-resolution mass spectra (HRMS) were recorded in the positive mode with a Bruker MicrOTOF-Q II XL spectrometer. Infrared spectra were recorded with a Nicolet IS 100 spectrometer. Melting points were recorded with a B-540 Büchi melting point apparatus.

Cross-Metathesis Reaction; General Procedure

To a solution of (2-chloromethylphenyl)carbamic acid allyl ester (**4b**; 1 equiv) and the corresponding alkene derivative **8** in anhydrous CH_2Cl_2 (0.1 M) under an argon atmosphere, was added second-generation Hoveyda–Grubbs catalyst (5 mol%). The reaction mixture was stirred at reflux under an argon atmosphere for 3 h before adding further second-generation Hoveyda–Grubbs catalyst (2 mol%) and the reaction mixture was stirred at reflux overnight. The solvent was removed in vacuo and the residue was purified by silica gel flash chromatography (PE–EtOAc, 9:1) to afford the desired compound **7**.

Cinnamyl (*E*)-(2-Chloromethylphenyl)carbamate (7a)

Yield: 157 mg [37%; isolated from **4b** (305 mg)]; white solid; mp 70–74 °C.

IR (neat): 3286, 3025, 1689, 1590, 1530, 1458, 1297, 1246, 966 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.86 (s, 1 H), 7.43–7.24 (m, 7 H), 7.11 (dd, *J* = 7.5 Hz, 1 H), 6.99 (s, 1 H), 6.72 (d, *J* = 15.4 Hz, 1 H), 6.36 (dt, *J* = 6.6, 15.4 Hz, 1 H), 4.85 (dd, *J* = 1.3, 6.6 Hz, 2 H), 4.63 (s, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 160.7, 136.8, 136.3, 134.6, 132.7, 130.3, 130.2, 128.8, 128.3, 126.8, 124.6, 123.4, 66.3, 44.2.

HRMS (ESI): *m*/*z* [M + Na^+] calcd for $C_{17}H_{16}ClNNaO_2$: 324.0762; found: 324.0766.

***p*-Trifluoromethylcinnamyl (*E*)-(2-Chloromethylphenyl)carbamate (7b)**

Yield: 104 mg [32%; isolated from **4b** (200 mg)]; beige solid; mp 102–104 °C.

IR (neat): 3273, 2923, 1697, 1533, 1330, 1249, 1127, 1067 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.87 (d, *J* = 7.6 Hz, 1 H), 7.59 (d, *J* = 8.4 Hz, 2 H), 7.51 (d, *J* = 8.4 Hz, 2 H), 7.44–7.35 (m, 1 H), 7.30 (dd, *J* = 1.4, 7.6 Hz, 1 H), 7.12 (t, *J* = 7.6 Hz, 1 H), 7.00 (br s, 1 H), 6.74 (d, *J* = 16.0 Hz, 1 H), 6.45 (dt, *J* = 6.2, 16.0 Hz, 1 H), 4.87 (dd, *J* = 1.3, 6.2 Hz, 2 H), 4.63 (s, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 153.7, 137.1, 136.7, 132.7, 130.3, 130.2, 129.9, 129.2, 125.5, 124.8, 124.7, 123.3, 122.4, 65.7, 44.1.

^{19}F NMR (282 MHz, $CDCl_3$): δ = –63.2.

HRMS (ESI): *m*/*z* [M + Na^+] calcd for $C_{18}H_{15}ClF_3NNaO_2$: 392.0636; found: 392.0624.

***m*-Trifluoromethylcinnamyl (*E*)-(2-Chloromethylphenyl)carbamate (7c)**

Yield: 107 mg [63%; isolated from **4b** (105 mg)]; beige solid; mp 83–84 °C.

IR (neat): 3282, 1694, 1591, 1532, 1458, 1336, 1299, 1251, 1165, 1120, 967 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.87 (d, *J* = 7.9 Hz, 1 H), 7.45–7.59 (m, 4 H), 7.39 (dd, *J* = 7.5, 7.9 Hz, 1 H), 7.30 (d, *J* = 7.5 Hz, 1 H), 7.09 (dd, *J* = 7.5, 7.5 Hz, 1 H), 6.99 (br s, 1 H), 6.74 (d, *J* = 15.8 Hz, 1 H), 6.43 (dt, *J* = 6.4, 15.8 Hz, 1 H), 4.87 (d, *J* = 6.4 Hz, 2 H), 4.63 (s, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 153.7, 137.1, 136.7, 132.7, 130.3, 130.2, 129.9, 129.2, 125.5, 124.8, 124.7, 123.3, 122.4, 65.7, 44.1.

^{19}F NMR (282 MHz, $CDCl_3$): δ = –63.2.

HRMS (ESI): *m*/*z* [M + Na^+] calcd for $C_{18}H_{15}ClF_3NNaO_2$: 392.0636; found: 392.0624.

2-Heptenyl (*E*)-(2-Chloromethylphenyl)carbamate (7d)
Yield: 182 mg [49%; isolated from **4b** (298 mg)]; white foam.

IR (neat): 2928, 1736, 1591, 1524, 1455, 1214 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.84 (d, *J* = 7.6 Hz, 1 H), 7.36 (dd, *J* = 7.6, 7.6 Hz, 1 H), 7.27 (d, *J* = 7.6 Hz, 1 H), 7.10 (dd, *J* = 7.6, 7.6 Hz, 1 H), 6.92 (s, 1 H), 5.83 (dt, *J* = 6.6, 15.5 Hz, 1 H), 5.64 (dt, *J* = 6.8, 15.5 Hz, 1 H), 4.62 (d, *J* = 6.6 Hz, 2 H), 4.61 (s, 2 H), 2.07 (dt, *J* = 6.8, 6.8 Hz, 2 H), 1.27–1.39 (m, 4 H), 0.90 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 153.8, 137.2, 136.9, 130.2, 130.1, 124.5, 123.9, 66.5, 44.1, 32.1, 31.1, 22.3, 14.0.

HRMS (ESI): *m*/*z* [M + Na^+] calcd for $C_{15}H_{20}ClNNaO_2$: 304.1075; found: 304.1069.

2-Nonenyl (*E*)-(2-Chloromethylphenyl)carbamate (7e)
Yield: 279 mg [62%; isolated from **4b** (327 mg)]; white foam.

IR (neat): 3296, 2927, 2855, 1728, 1591, 1526, 1456, 1214 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.85 (d, *J* = 7.5 Hz, 1 H), 7.37 (dd, *J* = 7.5, 7.5 Hz, 1 H), 7.27 (d, *J* = 7.5 Hz, 1 H), 7.09 (dd, *J* = 7.5, 7.5 Hz, 1 H), 6.92 (s, 1 H), 5.83 (dt, *J* = 6.6, 15.2 Hz, 1 H), 5.64 (dt, *J* = 6.4, 15.2 Hz, 1 H), 4.62 (d, *J* = 6.6 Hz, 2 H), 4.61 (s, 2 H), 2.10 (m, 2 H), 1.29–1.40 (m, 8 H), 0.89 (t, *J* = 6.8 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 153.8, 137.2, 137.1, 130.2, 130.1, 124.5, 123.9, 66.5, 44.1, 32.4, 31.8, 28.9, 22.7, 14.2.

HRMS (ESI): *m*/*z* [M + Na^+] calcd for $C_{17}H_{24}ClNNaO_2$: 332.1388; found: 332.1387.

4-Oxopent-2-enyl (*E*)-(2-Chloromethylphenyl)carbamate (7f)
Yield: 330 mg [80%; isolated from **4b** (347 mg)]; brown foam.

IR (neat): 3356, 1708, 1670, 1592, 1526, 1456, 1298, 1232, 979 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.82 (d, *J* = 7.9 Hz, 1 H), 7.38 (td, *J* = 1.5, 7.9 Hz, 1 H), 7.30 (dd, *J* = 1.5, 7.6 Hz, 1 H), 7.12 (td, *J* = 7.6, 1 H), 7.07 (s, 1 H), 6.82 (dt, *J* = 4.7, 16.1 Hz, 1 H), 6.31 (d, *J* = 16.1 Hz, 1 H), 4.88 (dd, *J* = 1.9, 4.7 Hz, 2 H), 4.63 (s, 2 H), 2.30 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 197.9, 153.8, 140.2, 131.1, 130.3, 130.2, 63.8, 44.0, 27.5.

HRMS (ESI): *m*/*z* [M + Na^+] calcd for $C_{13}H_{14}ClNNaO_3$: 290.0554; found: 290.0561.

4-Oxo-4-toluylbut-2-enyl (*E*)-(2-Chloromethylphenyl)carbamate (7g)
Yield: 217 mg [71%; isolated from **4b** (200 mg)]; beige solid; mp 116–117 °C.

IR (neat): 3263, 1692, 1668, 1530, 1295, 1251, 1088, 960 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.89 (d, *J* = 8.2 Hz, 2 H), 7.85 (s, 1 H), 7.46–7.38 (m, 1 H), 7.34 (dd, *J* = 7.8, 1.4 Hz, 1 H), 7.32–7.28 (m, 3 H), 7.20–7.13 (m, 2 H), 7.07 (dt, *J* = 4.2, 15.5 Hz, 1 H), 4.99 (dd, *J* = 4.2, 1.2 Hz, 2 H), 4.67 (s, 2 H), 2.44 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 189.6, 153.3, 144.2, 140.8, 136.5, 134.9, 130.31, 130.25, 129.5, 128.9, 126.2, 125.0, 123.3, 64.4, 44.1, 21.8.

HRMS (ESI): *m*/*z* [M + Na^+] calcd for $C_{19}H_{18}ClNNaO_3$: 366.0867; found: 366.0868.

Diels–Alder Reaction; General Procedure
To a solution of ester **7** (1 equiv) in anhydrous CH_2Cl_2 (0.1 M) was added tripotassium phosphate (5 equiv). The reaction mixture was stirred at r.t. under a nitrogen atmosphere for 7 d. After the excess of K_3PO_4 was filtered off over Celite, the solvent was removed in vacuo and the residue was purified by silica gel flash chromatography (PE–EtOAc, 8:2) to afford the desired tetrahydroquinoline derivatives **9**.

4-Phenyl-3,3a,4,5-tetrahydrooxazolo[3,4-*a*]quinolin-1-one (9a)
Yield: 63 mg [56%; isolated from **7a** (133 mg)]; white solid; mp 138–139 °C.

IR (neat): 2922, 1753, 1493, 1396, 1218, 1136, 756 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.22 (d, *J* = 8.3 Hz, 1 H), 7.14–7.35 (m, 6 H), 7.09 (d, *J* = 7.3 Hz, 1 H), 7.00 (dd, *J* = 7.3, 7.3 Hz, 1 H), 4.21 (m, 2 H), 3.92 (t, *J* = 7.7 Hz, 1 H), 3.03 (m, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 154.4, 140.5, 134.6, 129.4, 129.1, 128.1, 127.6, 127.5, 125.2, 123.7, 118.4, 66.3, 58.4, 43.7, 35.9.

HRMS (ESI): *m*/*z* [M + H^+] calcd for $C_{17}H_{16}NO_2$: 266.1176; found: 266.1164.

4-(*p*-Trifluoromethyl)phenyl-3,3a,4,5-tetrahydrooxazolo [3,4-*a*]quinolin-1-one (9b)
Yield: 42 mg [45%; isolated from **7b** (102 mg)]; white solid; mp 211–213 °C.

IR (neat): 2923, 1755, 1494, 1398, 1325, 1125, 1067 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.29 (d, *J* = 8.3 Hz, 1 H), 7.48 (d, *J* = 8.0 Hz, 2 H), 7.36 (d, *J* = 8.0 Hz, 2 H), 7.32 (dd, *J* = 7.5, 8.3 Hz, 1 H), 7.16 (d, *J* = 7.5 Hz, 1 H), 7.08 (dd, *J* = 7.5, 7.5 Hz, 1 H), 4.32 (m, 2 H), 3.97 (t, *J* = 7.5 Hz, 1 H), 3.15 (m, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 154.4, 140.5, 134.6, 129.9, 129.1, 128.1, 127.8, 126.5, 124.6, 123.9, 118.6, 66.0, 58.2, 43.7, 35.9.

^{19}F NMR (282 MHz, $CDCl_3$): δ = –63.1.

HRMS (ESI): *m*/*z* [M + H^+] calcd for $C_{18}H_{15}F_3NO_2$: 334.1049; found: 334.1047.

4-(*m*-Trifluoromethyl)phenyl-3,3a,4,5-tetrahydrooxazolo[3,4-*a*]quinolin-1-one (9c)
Yield: 57 mg [66%; isolated from **7c** (95 mg)]; beige solid; mp 181–182 °C.

IR (neat): 2924, 2846, 1737, 1495, 1399, 1333, 1219, 1122, 1073 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.29 (d, *J* = 7.5 Hz, 1 H), 7.62 (d, *J* = 7.9 Hz, 1 H), 7.55 (dd, *J* = 7.5, 7.9 Hz, 1 H), 7.48 (s, 1 H), 7.43 (d, *J* = 7.5 Hz, 2 H), 7.16 (d, *J* = 7.5 Hz, 1 H), 7.08 (dd, *J* = 7.5, 7.5 Hz, 1 H), 4.34 (m, 2 H), 3.97 (t, *J* = 7.5 Hz, 1 H), 3.12 (m, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 154.4, 140.5, 134.5, 131.1, 130.0, 129.1, 127.7, 124.6, 124.3, 123.9, 118.5, 66.0, 58.1, 43.6, 35.9.

^{19}F NMR (282 MHz, $CDCl_3$): δ = –63.1.

HRMS (ESI): *m*/*z* [M + H^+] calcd for $C_{18}H_{15}F_3NO_2$: 334.1049; found: 334.1056.

4-Butyl-3,3a,4,5-tetrahydrooxazolo[3,4-*a*]quinolin-1-one (9d)
Yield: 18 mg [11%; isolated from **7d** (188 mg)]; yellow oil.

IR (neat): 2956, 2927, 1745, 1493, 1459, 1401, 1224, 1135, 969 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.09 (d, *J* = 8.0 Hz, 1 H), 7.22 (d, *J* = 8.0 Hz, 1 H), 7.13 (d, *J* = 7.5 Hz, 1 H), 7.04 (td, *J* = 1.1, 7.5 Hz,

1 H), 4.50 (t, *J* = 8.0 Hz, 1 H), 4.39–4.27 (m, 1 H), 4.26 (dd, *J* = 6.3, 8.0 Hz, 1 H), 3.01 (dd, *J* = 5.0, 16.8 Hz, 1 H), 2.86 (dd, *J* = 2.1, 16.8 Hz, 1 H), 1.95 (ddd, *J* = 2.1, 5.0, 10.2 Hz, 1 H), 1.51–1.01 (m, 6 H), 0.87 (t, *J* = 7.0 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 155.1, 135.0, 130.1, 127.2, 123.94, 123.85, 118.9, 64.2, 57.6, 33.2, 31.6, 29.9, 24.2, 22.9, 14.2.

HRMS (ESI): *m*/*z* [M + Na^+] calcd for $C_{15}H_{19}NNaO_2$: 268.1308; found: 268.1309.

4-Hexyl-3,3a,4,5-tetrahydrooxazolo[3,4-*a*]quinolin-1-one (9e)
Yield: 19 mg [8%; isolated from **7e** (269 mg)]; yellow oil.

IR (neat): 2927, 1746, 1493, 1401, 1224, 1136, 963 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.09 (d, *J* = 8.2 Hz, 1 H), 7.27–7.20 (m, 1 H), 7.12 (d, *J* = 7.5 Hz, 1 H), 7.04 (td, *J* = 1.1, 7.5 Hz, 1 H), 4.50 (t, *J* = 8.0 Hz, 1 H), 4.36–4.29 (m, 1 H), 4.26 (dd, *J* = 6.4, 8.0 Hz, 1 H), 3.01 (dd, *J* = 5.1, 16.9 Hz, 1 H), 2.85 (dd, *J* = 1.7, 16.9 Hz, 1 H), 1.95 (ddd, *J* = 1.7, 5.1, 10.2 Hz, 1 H), 1.52–0.97 (m, 10 H), 0.86 (t, *J* = 6.9 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 155.1, 135.0, 130.1, 127.2, 123.94, 123.86, 118.9, 64.2, 57.6, 33.2, 31.9, 31.7, 29.5, 27.6, 24.5, 22.7, 14.2.

HRMS (ESI): *m*/*z* [M + H^+] calcd for $C_{17}H_{24}NO_2$: 274.1802; found: 274.1805.

4-Acetyl-3,3a,4,5-tetrahydrooxazolo[3,4-*a*]quinolin-1-one (9f)
Yield: 122 mg [71%; isolated from **7f** (198 mg)]; white solid; mp 161–162 °C.

IR (neat): 2910, 1747, 1708, 1583, 1499, 1460, 1398, 1318, 1254, 973 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.26 (d, *J* = 8.0 Hz, 1 H), 7.27 (t, *J* = 8.0 Hz, 1 H), 7.17 (d, *J* = 7.4 Hz, 1 H), 7.12–7.00 (m, 1 H), 4.78 (t, *J* = 8.8 Hz, 1 H), 4.24 (q, *J* = 8.5 Hz, 1 H), 3.99 (t, *J* = 8.8 Hz, 1 H), 3.21–3.38 (m, 1 H), 2.98–2.85 (m, 2 H), 2.32 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 207.7, 154.4, 134.5, 129.1, 127.9, 123.8, 123.1, 118.5, 67.2, 54.7, 50.7, 30.5, 28.7.

HRMS (ESI): *m*/*z* [M + Na^+] calcd for $C_{13}H_{13}NNaO_3$: 254.0788; found: 254.0783.

4-(*p*-Toluyl)carbonyl-3,3a,4,5-tetrahydrooxazolo[3,4-*a*]quinolin-1-one (9g)
Yield: 119 mg [62%; isolated from **7g** (214 mg)]; white solid; mp 228–229 °C.

IR (neat): 2920, 1747, 1667, 1605, 1494, 1403, 1309, 1227, 1142, 972 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.27 (d, *J* = 7.9 Hz, 1 H), 7.88 (d, *J* = 8.2 Hz, 2 H), 7.37–7.27 (m, 3 H), 7.12–7.01 (m, 2 H), 4.82–4.68 (m, 1 H), 4.54 (dt, *J* = 8.0, 10.0 Hz, 1 H), 4.01 (dd, *J* = 8.0, 9.0 Hz, 1 H), 3.80 (ddd, *J* = 5.0, 10.1, 12.8 Hz, 1 H), 3.26 (dd, *J* = 5.0, 16.7 Hz, 1 H), 3.01 (dd, *J* = 12.8, 16.7 Hz, 1 H), 2.45 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 199.5, 154.5, 145.6, 134.6, 132.9, 130.0, 129.0, 128.8, 127.9, 123.81, 123.76, 118.7, 66.9, 55.5, 45.5, 32.8, 21.9.

HRMS (ESI): *m*/*z* [M + Na^+] calcd for $C_{19}H_{17}NNaO_3$: 330.1101; found: 330.1096.

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