Gold-Catalyzed [2+2] Cyclization of Alkyne-propargylic Pivaloates to Fused Bicyclic Compounds

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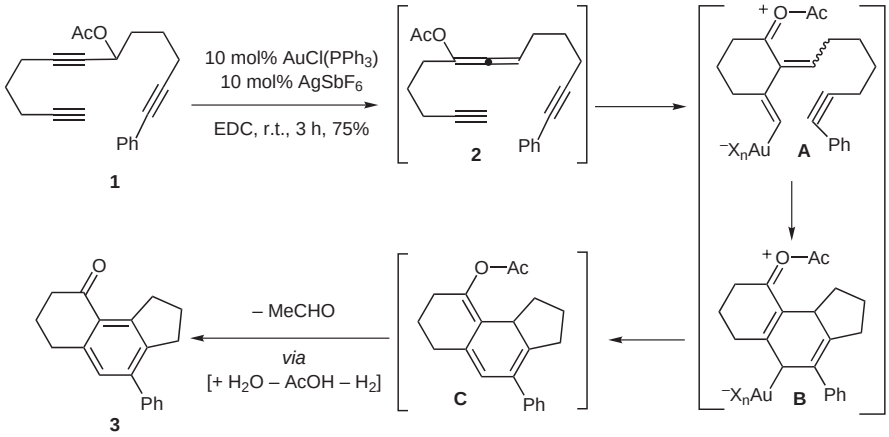
Abstract: We discovered a new and highly convenient gold-catalyzed cyclization of alkyne-propargylic pivaloates leading to fused bicyclic compounds.

Key words: gold, cyclization, pivaloate, catalyst, bicyclic compounds

Recent advances in gold-based alkyne activation led to develop new and efficient catalytic reactions applicable to the synthesis of complex molecules.[1] On the behalf of the excellent alkynophilicity of gold cations, terminal alkynes in the presence of a nucleophile could form gold–carbene complexes.[2] Internal alkynes are weakly activated enough to react with nucleophiles of alkenes or aldehydes. Phenyl-substituted alkynes, for example, might form weak π-complexes which underwent [2+2+2] cycloaddition with a pendent double bond and one double bond in the phenyl ring.[3] We became interested in gold-catalyzed chemistry of triynes containing a terminal, an internal (propargylic ester), and a phenyl-conjugated triple bond in the same molecule.

In this context, we recently reported gold-catalyzed cascade cyclization of the triyne **1** to the tricycle **3**.[4] Mechanistically, the allene **2**, the initial intermediate from **1** under the gold catalysis, would react with the terminal triple bond to form the gold-bound diene intermediate **A**, which would subsequently undergo [4+2] cycloaddition to **B**. The further conversion of **B** via demetalation (into **C**) and dehydrogenation afforded the tricycle **3** (Scheme 1). Yet its mechanism and the origin of hydrogen were not clear.

The present conditions toward a triyne **4a**, a homologue of **1a**, did not afford the expected tricycle, but exhibited a different mode of reactions to give the [3.2.0]-bicyclic system **7a**. Herein we wish to report our results on the scope and limitations of this new reaction leading to the [3.2.0] and [4.2.0] bicycles **7** (Scheme 2).[5] At first, we surveyed the reaction conditions including catalysts, solvent, and the reaction temperatures toward the substrate **4a** (Table 1). Sodium tetrachloroaurate ($NaAuCl_4$) was tested in three different solvents (entries 1–3). While $NaAuCl_4$ in either dichloromethane at 50 °C or 1,4-dioxane at 80 °C was ineffective, $NaAuCl_4$ in ethanol catalyzed **4a** into the allene intermediate **5a**, which was hydrolyzed to the corresponding enone **6a**. The same conversion into enone **6a** was also carried out by $AuBr_3$ in ethanol at 80 °C (entry 4). Both $AuCl/AgSbF_6$ and $AuCl_3/AgSbF_6$ as cooperative catalysts in dioxane at 50 °C led to decomposition of **4a**. To our delight, 5 mol% $AuCl(PPh_3)$ with $AgSbF_6$ as a cocatalyst in 1,2-dichloroethane (DCE) at room temperature converted **4a** into the bicyclo[3.2.0] compound **7a** in 72% yield (entry 7). Finally, we tested $PtCl_2$ as a catalyst but found to be ineffective for this reaction (entry 8). Next, we tested other structurally similar



Scheme 1

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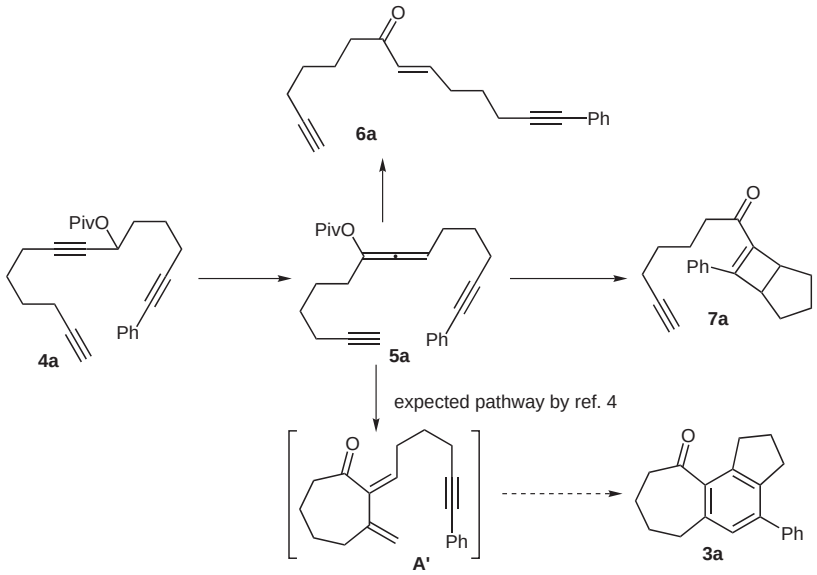


Scheme 2

Table 1 Cyclization of **4a** under Various Conditions

Entry	Catalyst (5 mol%)	Solvent	Temp (°C)	Time (h)	Product (yield, %)
1	$NaAuCl_4$	CH_2Cl_2	50	5	NR
2	$NaAuCl_4$	dioxane	80	5	NR
3	$NaAuCl_4$	EtOH	80	0.5	**6a** (75)
4	$AuBr_3$	EtOH	80	0.5	**6a** (74)
5	$AuCl/AgSbF_6$	dioxane	50	15	dec.
6	$AuCl_3/AgSbF_6$	dioxane	50	15	dec.
7	$AuCl(PPh_3)/AgSbF_6$	DCE	25	15	**7a** (72)
8	$PtCl_2$	toluene	100	15	NR

substrates (**4b**–**g** and **4h**–**j**) under the optimized conditions described in entry 7 in Table 1 (Table 2).[6]

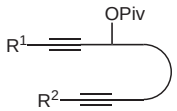
The substrates **4b**–**g** were smoothly transformed to the [3.2.0] bicycles **7b**–**g** in good yields. Substrate **4b**, possessing 6-phenylhex-1-ynyl at the R^1 position and phenyl group at the R^2 position furnished the desired product **7b** in 81% yield. The reactions proceeded smoothly, when the phenyl group (**4c**,**d**) and naphthyl group (**4e**,**f**) were located at the R^2 position, affording **4c**–**f** in 72–81% yield. Notably, the substrate **4g** containing a cyclohexyl ring at the R^2 position was successfully cyclized to **7g** in 72% yield.

The present conditions were successfully applied to the substrates **4h**–**j** affording bicyclo[4.2.0] compounds **7h**, **7i**, and **7j** in 65%, 55%, and 75% yields, respectively.

Next, we have extended further this reaction to two alkyne-pivaloate groups in a molecule linked by a phenyl group to obtain the corresponding dimeric bicycles for useful building blocks (Scheme 3). Both substrates **4k** and **4l** were prepared and cyclized under the present conditions to give the expected products **7k** and **7l** in 85% and 83% yields, respectively. Surprisingly, these cyclizations **4k**,**l** to **7k**,**l** seemed to proceed more easily in comparison to substrates **4a**–**j**; this might imply that the electron-withdrawing effect by the first cyclization might facilitate the second cyclization.

A possible mechanism for gold-catalyzed cyclization of alkyne-proparglic pivaloate **4a** to **7a** is proposed (Scheme 4).

Table 2 Gold(I)-Catalyzed Cyclization of Alkyne-pivaloates **4** to Bicyclo[m.2.0] Compounds **7** (Figure 1)

Substrates	Temp (°C)	Time (h)	Product	Yield (%)[a]
				
4b	80	15	**7b**	81
4c	40	1	**7c**	75
4d	40	1	**7d**	80
4e	25	1	**7e**	72
4f	25	1.5	**7f**	80
4g	25	2	**7g**	72
4h	40	2.5	**7h**	65
4i	40	15	**7i**	55
4j	25	15	**7j**	75

[a] All reactions were carried out 5 mol% of $AuCl(PPh_3)$ and $AgSbF_6$ in DCE.

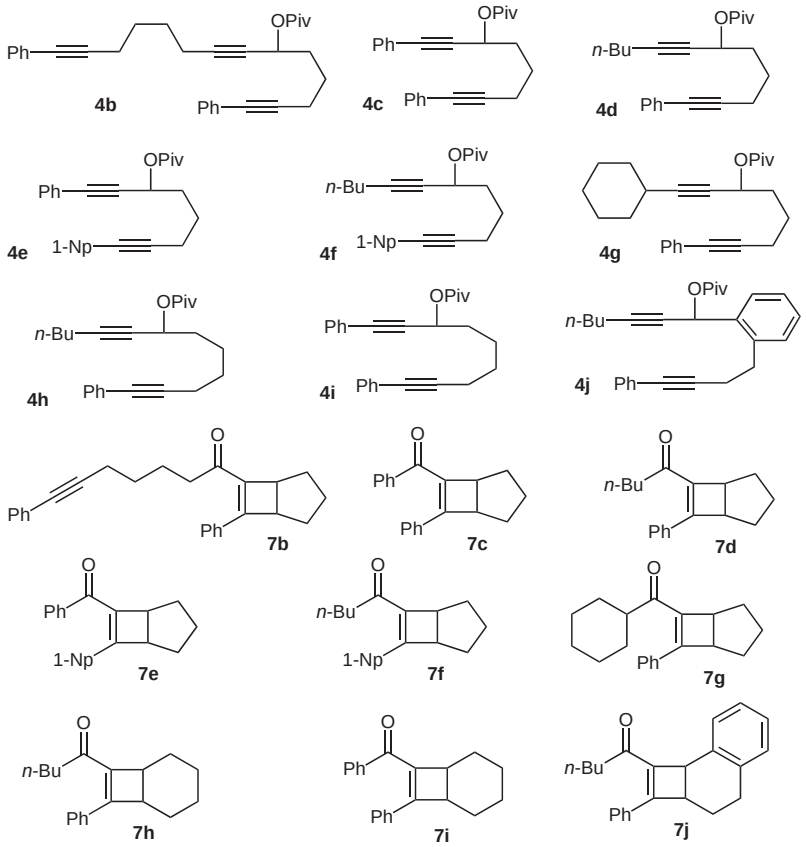
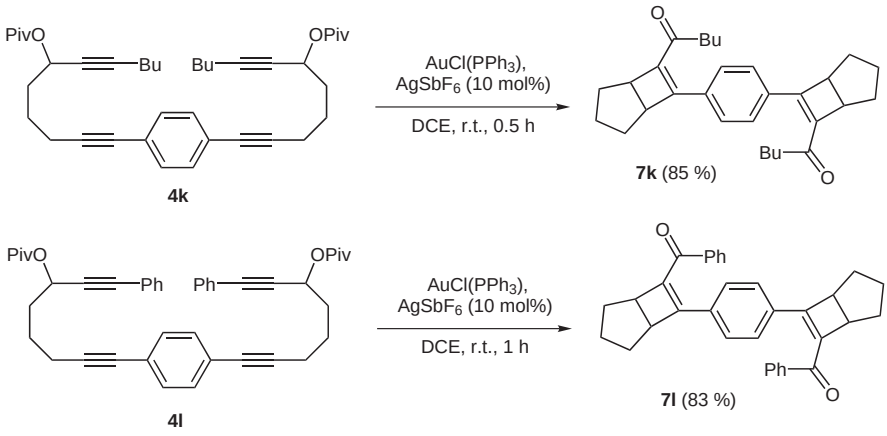


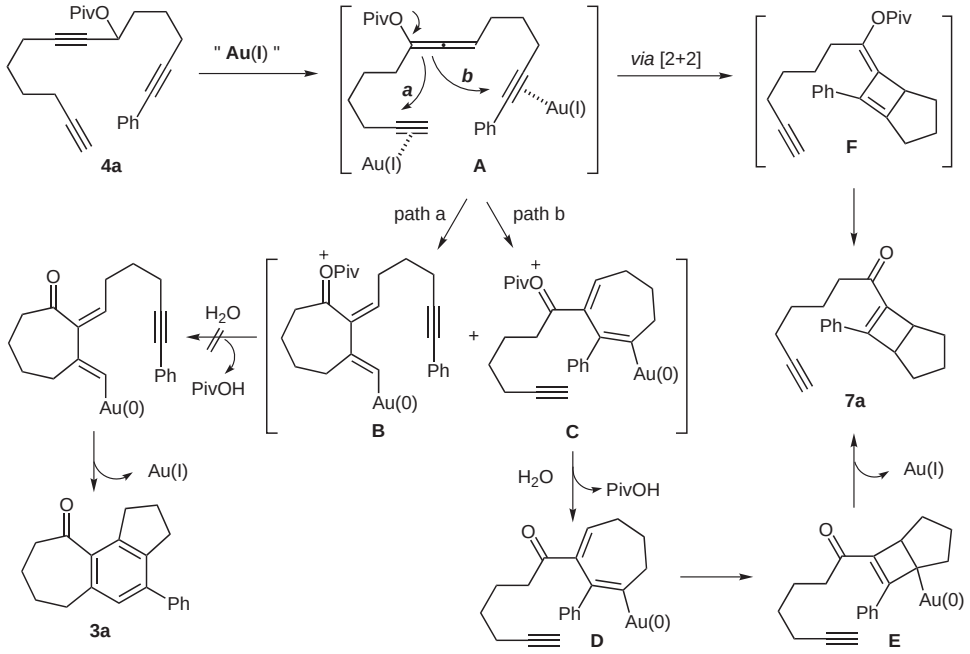
Figure 1



Scheme 3

Coordination of gold(I) to propargylic alkyne induced migration of the pivaloate to give the allene intermediate **A**. The allene **A** was expected to undergo condensation with one of the gold-activated triple bonds, path a and b. The isolation of **7a** and no formation of **3a** might suggest the intermediacy of **C** via path b. Intermediate **C** could eliminate pivaloic acid by addition of H_2O to form **D**. Finally, cyclization of **D** into **E** might be postulated, although such a cyclization is not known. Instead, the allene **A** could be directly cycloadded via a [2+2] pathway to give the intermediate **F**, which would afford the isolated product **7a** upon hydrolysis.

In conclusion, we discovered a highly convenient gold-catalyzed cyclization of alkyne-propargylic pivaloates leading to [m.2.0] bicyclic compounds, that could provide an easy access to valuable building blocks for polycyclic compounds.



Scheme 4

Acknowledgment

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(6) **Typical Experimental Procedure for Cyclization of 4a to 7a**

In a 5 mL new test tube were placed $AuCl(PPh_3)$ (7.0 mg, 14.0 μmol, 5 mol%) and $AgSbF_6$ (4.8 mg, 14 μmol) and added dried DCE (1.0 mL) under argon atmosphere. After being stirred for 10 min at 0 °C, a DCE solution (0.5 mL) of diyne-propargylic pivaloate **4a** (101.0 mg, 0.28 mmol) was added. The resulting mixture was stirred for 15 h at r.t. and the reaction was periodically monitored by TLC. Upon completion, the solvent was removed under vacuum and the crude product was subjected to flash column chromatography (SiO_2, *n*-hexane–EtOAc = 30:1) to afford the pure product **7a** as a colorless oil. All new compounds were fully characterized by ^1H NMR, ^{13}C NMR, IR, and HRMS (ESMS).

Compound **7a**: IR (NaCl): 3301, 3064, 2940, 2869, 1707, 1671, 1491, 1287 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.07–8.04 (m, 2 H), 7.42–7.37 (m, 3 H), 3.47 (q, *J* = 4.0 Hz, 1 H), 3.40 (q, *J* = 4.0 Hz, 1 H), 2.68–2.49 (m, 2 H), 2.22 (td, *J* = 7.0, 3.2 Hz, 2 H), 1.95 (t, *J* = 2.4 Hz, 1 H), 1.83–1.68 (m, 5 H), 1.66–1.54 (m, 3 H), 1.49–1.38 (m, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 197.13, 155.44, 136.26, 132.49, 130.25, 128.93, 128.35, 84.19, 68.46, 43.75, 43.28, 40.06, 28.01, 26.31, 26.07, 23.16, 22.72, 18.35. HRMS: *m/z* calcd for $C_{20}H_{22}ONa^+$: 301.3779; found: 301.3787.

Compound **7b**: IR (NaCl): 3059, 3030, 2931, 2853, 2225, 1736, 1670, 1560, 1175 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.06–8.04 (m, 2 H), 7.39–7.37 (m, 5 H), 7.28–7.24 (m, 3 H), 3.45 (q, *J* = 3.6 Hz, 1 H), 3.39 (q, *J* = 3.6 Hz, 1 H), 2.71–2.52 (m, 2 H), 2.44 (t, *J* = 7.6 Hz, 2 H), 1.86–1.77 (m, 4 H), 1.73–1.54 (m, 6 H), 1.48–1.38 (m, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 197.23, 155.39, 136.35, 132.55, 131.55, 130.23, 128.94, 128.35, 128.14, 127.49, 123.97, 89.87, 80.89, 43.78, 43.33, 40.17, 28.33, 26.34, 26.09, 23.18, 22.97, 19.35. HRMS: *m/z* calcd for $C_{26}H_{26}ONa^+$: 377.4733; found: 377.4778.

Compound **7c**: IR (NaCl): 3065, 3030, 2945, 2857, 2247, 1797, 1634, 1490, 1228, 1172 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.88 (d, *J* = 3.8 Hz, 2 H), 7.57–7.54 (m, 2 H), 7.49 (t, *J* = 7.2 Hz, 1 H), 7.38 (t, *J* = 7.2 Hz, 2 H), 7.28–7.23 (m, 3 H), 3.64–3.56 (m, 2 H), 1.87–1.78 (m, 2 H), 1.74–1.63 (m, 2 H), 1.52–1.46 (m, 1 H), 1.42–1.32 (m, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 191.46, 153.85, 138.08, 136.24, 132.54, 132.40, 129.54, 128.94, 128.69, 128.39, 128.19, 45.69, 44.53, 26.49, 26.27, 23.29 29. HRMS: *m/z* calcd for

$C_{20}H_{18}ONa^+$: 297.3461; found: 297.3462.
Compound **7d**: IR (NaCl): 3066, 2956, 2933, 2869, 2350, 1716, 1655, 1540, 1458 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.06–8.04 (m, 2 H), 7.40–7.37 (m, 3 H), 3.47–3.38 (m, 2 H), 2.64–2.46 (m, 2 H), 1.84–1.77 (m, 2 H), 1.74–1.56 (m, 5 H), 1.49–1.33 (m, 5 H), 0.92 (t, *J* = 7.2 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 197.87, 155.07, 136.52, 132.57, 130.15, 128.92, 128.32, 43.70, 43.34, 40.41, 26.32, 26.09, 25.80, 23.17, 22.43, 13.96. HRMS: *m/z* calcd for $C_{18}H_{22}ONa^+$: 277.3559; found: 277.3554.
Compound **7e**: IR (NaCl): 3058, 2942, 2859, 2252, 1747, 1636, 1578, 1445, 1334 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.96 (d, *J* = 8 Hz, 1 H), 7.74–7.69 (m, 2 H), 7.57 (d, *J* = 7.2 Hz, 2 H), 7.39–7.28 (m, 4 H), 6.93 (t, *J* = 7.6 Hz, 2 H), 3.86 (q, *J* = 3.6 Hz, 1 H), 3.68 (q, *J* = 3.6 Hz, 1 H), 2.31–2.27 (m, 1 H), 1.89–1.65 (m, 2 H), 1.86–1.77 (m, 2 H), 1.63–1.51 (m, 2 H), 1.44–1.34 (m, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 191.50, 154.83, 139.20, 137.60, 133.31, 131.96, 131.86, 130.83, 129.02, 128.95, 128.68, 128.20, 127.60, 127.01, 126.24, 125.79, 125.23, 124.89, 48.74, 45.71, 26.85, 25.58, 23.54. HRMS: *m/z* calcd for $C_{24}H_{20}ONa^+$: 347.4042; found: 347.4042.
Compound **7f**: IR (NaCl): 3056, 2956, 2930, 2858, 1655, 1506, 1460, 1391, 1198, 1026 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.97–7.84 (m, 3 H), 7.52–7.37 (m, 4 H), 3.62–3.50 (m, 2 H), 2.23–2.08 (m, 2 H), 2.04–2.01 (m, 1 H), 1.84–1.76 (m, 2 H), 1.61–1.58 (m, 2 H), 1.51–1.41 (m, 1 H), 1.38–1.26 (m, 4 H), 0.59 (t, *J* = 7.6 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 198.22, 155.35, 141.22, 133.55, 132.77, 130.74, 128.86, 128.51, 126.48, 126.20, 125.81, 125.41, 125.13, 48.87, 43.80, 39.96, 26.37, 26.23, 24.96, 23.47, 22.16, 13.52. HRMS: *m/z* calcd for $C_{22}H_{24}ONa^+$: 327.4146; found: 327.4145.
Compound **7g**: IR (NaCl): 3032, 2936, 2863, 2246, 1769, 1649, 1507, 1338 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.89–7.86 (m, 2 H), 7.54–7.47 (m, 3 H), 7.39–7.35 (m, 2 H), 7.26–7.24 (m, 1 H), 3.41–3.30 (m, 2 H), 2.06–1.96 (m, 1 H), 1.87–1.47 (m, 7 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 191.65, 157.03, 139.83, 138.07, 133.36, 132.40, 129.37, 128.86, 128.53, 128.41, 128.22, 39.68, 38.60, 24.10, 23.51, 18.82, 18.70. HRMS: *m/z* calcd for $C_{21}H_{20}ONa^+$: 311.3721; found: 311.3725.
Compound **7h**: IR (NaCl): 2961, 2860, 2255, 1794, 1714 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.01–7.98 (m, 2 H), 7.40–7.37 (m, 3 H), 3.19 (q, *J* = 6.0 Hz, 1 H), 3.13 (q, *J* = 5.6 Hz, 1 H), 2.62–2.43 (m, 2 H), 1.97–1.89 (m, 2 H), 1.78–1.68 (m, 2 H), 1.66–1.58 (m, 3 H), 1.57–1.42 (m, 4 H), 1.39–1.30 (m, 2 H), 1.27–1.22 (m, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 198.18, 158.27, 140.18, 133.32, 129.95, 128.78, 128.31, 40.80, 37.91, 37.56, 25.74, 23.94, 23.81, 22.43, 18.85, 18.70, 13.94. HRMS: *m/z* calcd for $C_{19}H_{24}ONa^+$: 291.3824; found: 291.3830.
Compound **7i**: IR (NaCl): 3051, 2905, 2322, 1745, 1678, 1487, 1145 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.04–8.02 (m, 2 H), 7.39–7.37 (m, 3 H), 3.46 (q, *J* = 3.6 Hz, 1 H), 3.41 (q, *J* = 3.6 Hz, 1 H), 2.69–2.64 (m, 1 H), 1.86–1.77 (m, 5 H), 1.74–1.68 (m, 2 H), 1.66–1.59 (m, 1 H), 1.50–1.41 (m, 3 H), 1.34–1.21 (m, 5 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 201.37, 155.99, 136.40, 132.64, 130.11, 128.85, 128.30, 47.53, 43.66, 43.56, 29.13, 28.13, 26.62, 26.19, 25.97, 25.87, 25.57, 23.18. HRMS: *m/z* calcd for $C_{20}H_{24}ONa^+$: 303.3932; found: 303.3930.
Compound **7j**: IR (NaCl): 3067, 3032, 2863, 2246, 1769, 1649, 1652, 1507, 1338 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.05–8.03 (m, 2 H), 7.43–7.41 (m, 3 H), 7.37–7.35 (m, 1 H), 7.23–7.15 (m, 2 H), 7.11–7.09 (m, 1 H), 4.21 (d, *J* = 4.8 Hz, 1 H), 3.79 (t, *J* = 4.8 Hz, 1 H), 2.61–2.49 (m, 2 H), 2.37–2.30 (m, 2 H), 1.65–1.50 (m, 2 H), 1.46–1.35 (m, 2 H), 1.30–1.21 (m, 2 H), 0.84 (t, *J* = 7.2 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 197.73, 155.56, 139.72, 137.17, 136.27, 132.32, 130.51, 130.02, 129.29, 129.00, 128.91, 128.80, 128.69, 128.60, 126.58, 126.39, 43.16, 41.42, 39.84, 26.48, 25.67, 39.84, 26.48, 25.67, 25.41, 22.53, 14.12. HRMS: *m/z* calcd for $C_{23}H_{24}ONa^+$: 339.4253; found: 339.4254.
Compound **7k**: IR (NaCl): 3065, 2949, 2845, 2358, 2249, 1728, 1634, 1598, 1579, 1501, 1446, 1289 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.05 (s, 4 H), 3.46 (q, *J* = 3.2 Hz, 2 H), 3.40 (q, *J* = 4 Hz, 2 H), 2.66–2.46 (m, 4 H), 1.80 (td, *J* = 13.6, 5.2 Hz, 4 H), 1.72–1.57 (m, 8 H), 1.47–1.30 (m, 8 H), 0.92 (t, *J* = 7.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 197.79, 154.25, 137.53, 133.82, 128.86, 43.68, 43.54, 40.47, 29.68, 26.35, 25.81, 23.16, 22.43, 13.98. HRMS: *m/z* calcd for $C_{30}H_{38}O_2Na^+$: 453.6107; found: 453.6104.
Compound **7l**: IR (NaCl): 2955, 2859, 2357, 1746, 1667, 1588, 1504, 1457, 1177 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.87 (d, *J* = 7.6 Hz, 4 H), 7.52–7.36 (m, 10 H), 3.62 (q, *J* = 3.2 Hz, 2 H), 3.54 (q, *J* = 3.6 Hz, 2 H), 1.82–1.62 (m, 8 H), 1.41–1.31 (m, 4 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 191.29, 137.31, 133.29, 128.90, 128.53, 128.47, 120.62, 45.92, 44.43, 26.48, 26.27, 23.27. HRMS: *m/z* calcd for $C_{34}H_{30}O_2Na^+$: 493.5900; found: 493.5889.