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Rotamer-dependent chemiluminescence in the intramolecular charge-transfer-induced decomposition of bicyclic dioxetanes bearing a hydroxyaryl group

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ABSTRACT

Base-induced chemiluminescent decomposition of acylamino-substituted dioxetane **1b** bearing a 3-hydroxyphenyl group proceeded according to dual phase kinetics due to *syn*–*anti* isomerism of the aryl group. For dioxetane **7** bearing a 6-hydroxynaphthalen-2-yl group, *syn*- and *anti*-rotamers were each isolated and their structures were determined by X-ray single crystallographic analysis. Both rotamers underwent base-induced decomposition accompanied by the emission of red light to exclusively give the same keto imide **8**. However, a marked difference in chemiluminescence efficiency was observed between *anti*-**7** and *syn*-**7**.

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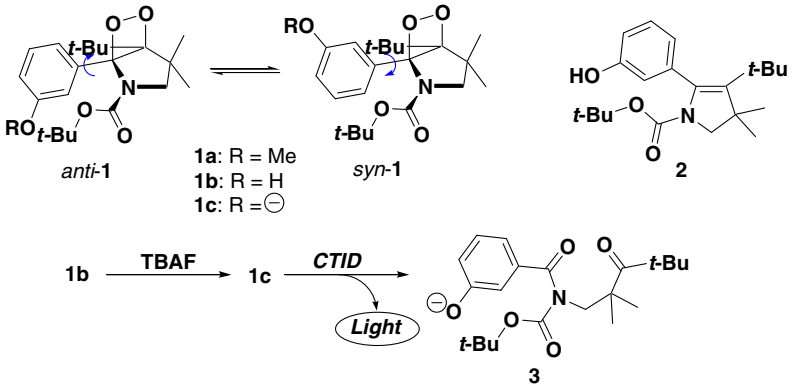
Dioxetanes bearing a phenoxide anion as an electron donor undergo intramolecular charge-transfer-induced decomposition (CTID) accompanied by the emission of light.[1,2] This phenomenon has received considerable attention due to interest in the mechanism related to bioluminescence and chemiluminescence and in a possible application to high-performance biological and clinical analysis.[3–6] Thus, extensive research has been conducted to elucidate the singlet-chemiexcitation process[7–12] as well as to develop highly effective dioxetane-based chemiluminescence systems. However, it is still unclear how chemiluminescence is related to the structure of dioxetanes. Thermally persistent acylamino-substituted dioxetane **1a** has very recently been synthesized as a new class of dioxetanes.[13] One of the most intriguing features of **1a** was that a pair of *syn*–*anti* rotamers was observed at room temperature by NMR analysis, though neither could be isolated (Scheme 1). This finding prompted us to realize CTID-active acylamino-substituted dioxetanes that exhibit such rotational isomerism and to investigate their chemiluminescence properties,



Scheme 1. Rotamers of dioxetane **1** and CTID of **1b**.

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with the expectation that this could shed light on the relationship between the structure of dioxetanes and their chemiluminescence properties.

A CTID-active dioxetane, 3-hydroxyphenyl analog **1b**, was easily synthesized by the singlet oxygenation of dihydropyrrole **2**. ^{1}H NMR and ^{13}C NMR spectra showed that the dioxetane existed as a mixture of *syn*-**1b** and *anti*-**1b** (55:45), similar to the case of **1a**.[14] We first investigated whether or not the rotational isomerism was reflected in the CTID of **1b**. When **1b** was treated with a large excess of tetrabutylammonium fluoride (TBAF) in DMSO at 25 °C,[15] **1b** underwent CTID accompanied by the emission of yellow light (maximum wavelength $\lambda_{max}^{CL} = 571$ nm, chemiluminescence efficiency $\Phi^{CL} = 8.5 \times 10^{-3}$).[16,17] After neutralization, spent reaction mixture gave a hydroxy form of **3** in high yield. Therefore, the CTID of **1b** was thought to proceed through unstable oxidophenyldioxetane **1c** to give keto imide **3** in the excited state (Scheme 1).

The time course of the CTID is shown in Figure 1, from which we can see that **1b** underwent a dual phase decomposition, consisting of fast and slow reactions. Kinetic analysis revealed that both reactions proceeded according to pseudo-first order kinetics, and their rate constants k_{fast}^{CTID} and k_{slow}^{CTID} were estimated to be 0.70 s^{-1} and 0.040 s^{-1}, respectively. The CTID of **1b** contrasted sharply with that of analog **4** bearing a 4-hydroxyphenyl, which did not show *syn*–*anti* isomerism (Fig. 2). Dioxetane **4** decomposed simply in a single

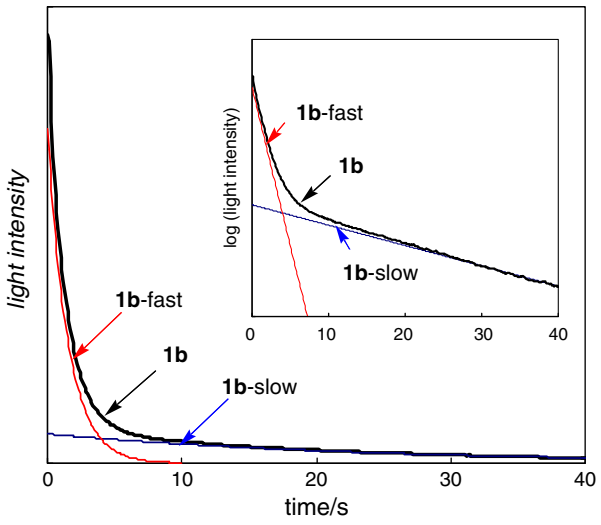


Figure 1. Time course of CTID of **1b** in TBAF/DMSO system at 25 °C.

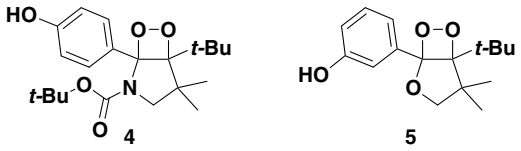
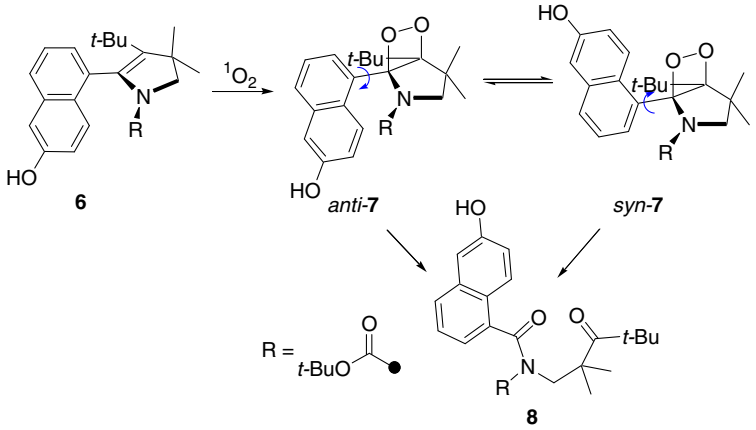


Figure 2. Dioxetane **4** and oxygen-substituted dioxetane **5**.

phase according to pseudo-first order kinetics to give blue light ($k^{CTID} = 0.14$ s^{-1}, $\lambda_{max}^{CL} = 471$ nm, $\Phi^{CL} = 1.1 \times 10^{-7}$). Such simple single-phase decomposition has been reported as a rather normal feature for most known CTID-active dioxetanes, as represented by furan-analog **5**, for which the rotational isomerism has hardly been observed.[18] These facts suggest that one rotamer (*syn* or *anti*) decomposed rapidly while the other decomposed slowly for the CTID of **1b**. However, it is not clear whether the rotamer with k_{slow}^{CTID} decomposed directly or first isomerized to another rotamer that then decomposed: the *syn*-*anti* isomerism of **1** occurred too fast for it to be isolated, but slow enough for it to be observed in NMR.

Our next attempt was based on the idea that the introduction of a bulky aryl group, such as naphthalen-1-yl, in place of 3-hydroxyphenyl, into the dioxetane skeleton **1** may suppress the *syn*–*anti* isomerism. When a solution of *N*-Boc-5-(6-hydroxynaphthalen-1-yl)-2,3-dihydropyrrole **6** in CH_2Cl_2 was irradiated with a Na-lamp together with a catalytic amount of tetraphenylporphin under an O_2 atmosphere at 0 °C for 1 h, 1,2-addition of singlet oxygen onto **6** proceeded smoothly (Scheme 2). ^{1}H NMR analysis of the photolysate showed that dioxetane *anti*-**7** formed exclusively. Chromatographic purification gave pure *anti*-**7** as pale yellow granules, mp 181.5–184.0 °C (dec.) (from AcOEt), which gave satisfactory ^{1}H NMR, ^{13}C NMR, IR, and mass spectral data.[19] The stereochemistry of *anti*-**7** was finally determined by X-ray single crystallographic analysis, as illustrated in Figure 3a.[20]

When *anti*-**7** was heated in toluene-d_8 at 110 °C for 10 min, ^{1}H NMR analysis showed that *anti*-**7** isomerized into *syn*-**7** to give a mixture of *anti*-**7**:*syn*-**7** = 72:28, and decomposed concomitantly to give ca. 5% of keto ester **8**. Prolonged heating of *anti*-**7** did not change the ratio of rotamers but increased decomposition product **8**. The rotamer *syn*-**7** could be isolated in pure form by column chromatography as pale yellow prisms, mp 148.0–148.5 °C (from benzene/CH_2Cl_2).[21] The structure of *syn*-**7** was determined by ^{1}H NMR, ^{13}C NMR, IR, and mass spectral analyses, and finally by X-ray single crystallographic analysis, as illustrated in Figure 3b.[20] Rotamer *syn*-**7** gave a mixture of *anti*-**7**:*syn*-**7** with the same ratio as with *anti*-**7** along with a small amount of **8** on heating at



Scheme 2.

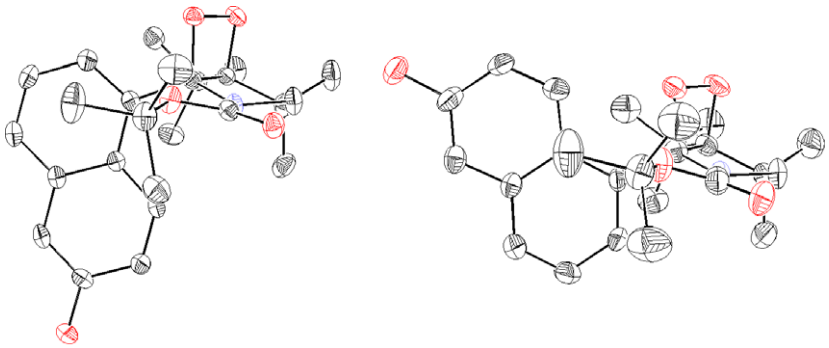


Figure 3. ORTEP views of dioxetane **7**.

110 °C in toluene-d_8. However, isomerization between *anti*-**7** and *syn*-**7** was hardly observed at room temperature. The present results provide a unique example of the successful isolation of rotamers for aryl-substituted dioxetane.

When *anti*-**7** was treated with a large excess of TBAF at 25 °C,[22] *anti*-**7** underwent CTID following pseudo-first order kinetics to emit red light with $\lambda_{max}^{CL} = 678$ nm, $\Phi^{CL} = 2.8 \times 10^{-4}$, and $k^{CTID} = 3.2 \times 10^{-2}\ s^{-1}$. The CTID of *syn*-**7** also proceeded to give red light upon similar treatment with TBAF. However, Φ^{CL} for *syn*-**7** was only 1/19 of that for *anti*-**7**, and the rate of CTID was considerably slower than that for *anti*-**7** (k^{CTID}:*syn*-**7**/*anti*-**7** = 1/6), as summarized in Table 1. The chemiluminescence spectrum for *syn*-**7** was also different to some extent from that for *anti*-**7**, as illustrated in Figure 4 and Table 1. Next, we examined the CTIDs of rotamers in acetonitrile to confirm whether rotamer-dependent chemiluminescent decomposition also occurred in a solvent other than DMSO. As shown in Table 1, a marked difference in Φ^{CL} was also observed between *syn*-**7** and *anti*-**7** in acetonitrile.

The results described above raise important questions related to the singlet-chemiexcitation mechanism for CTID of dioxetanes. It is not surprising that k^{CTID} changed depending on the conformation of an aromatic ring, since the rate of CTID has often been reported to be affected by the structure of dioxetanes.[5,6] However, we did not expect the marked difference in chemiluminescence efficiency between *syn*-**7** and *anti*-**7**. The difference in the chemiluminescence spectra between *syn*-**7** and *anti*-**7** is also rather unusual for a homogeneous system, although both rotamers gave the same keto imide **8**.

Excited oxido anion **9** was thought to be an emitter produced from both *anti*-**7** and *syn*-**7** in CTID, since **8** was isolated in high yields from both spent reaction mixtures after neutralization. The fluorescence spectrum of authentic oxido anion **9** generated from **8** in situ coincided with the chemiluminescence spectrum of *syn*-**7** in both solvent systems (DMSO and acetonitrile): maximum wavelength of fluorescence $\lambda_{max}^{fl} = 688$ nm, and fluorescence efficiency $\Phi^{fl} = 1.2 \times 10^{-3}$ in DMSO, $\lambda_{max}^{fl} = 700$ nm, and $\Phi^{fl} = 5.8 \times 10^{-4}$ in acetonitrile. Thus, the singlet-chemiexcitation efficiency $\Phi_s = \Phi^{CL}/\Phi^{fl}$ for the CTID of *syn*-**7** was estimated to be 0.013 in the DMSO system and 0.014 in the acetonitrile system.

Table 1
TBAF-induced chemiluminescent decomposition of dioxetanes **1b**, **4**, and rotamers of dioxetane *anti*-**7** and *syn*-**7**[a]

Dioxetane	Solvent	λ_{max}^{CL} (nm)	Φ^{CL}[b]	k^{CTID} (s^{-1})
1b	DMSO	571	8.5×10^{-3}	0.70, 0.040
4	DMSO	471	1.1×10^{-7}	0.14
anti-**7**	DMSO	678	2.8×10^{-4}	3.2×10^{-2}
syn-**7**	DMSO	688	1.5×10^{-5}	5.7×10^{-3}
anti-**7**	Acetonitrile	690	1.0×10^{-4}	6.5×10^{-3}
syn-**7**	Acetonitrile	701	8.3×10^{-6}	6.5×10^{-4}

[a] All reactions were carried out at 25 °C.
[b] Chemiluminescence efficiencies were estimated based on the value for 3-(3-*tert*-butyldimethylsiloxy)phenyl-4-adamantylidene-4-methoxy-1,2-dioxetane.[17]

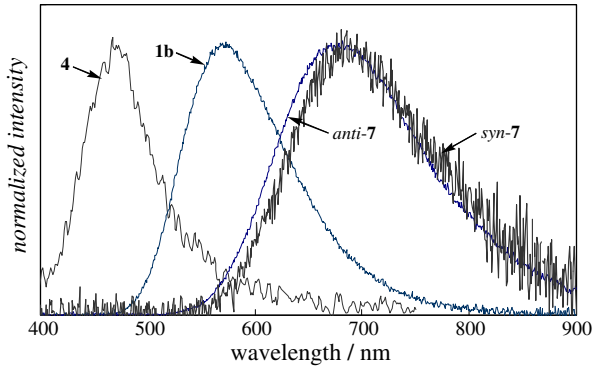
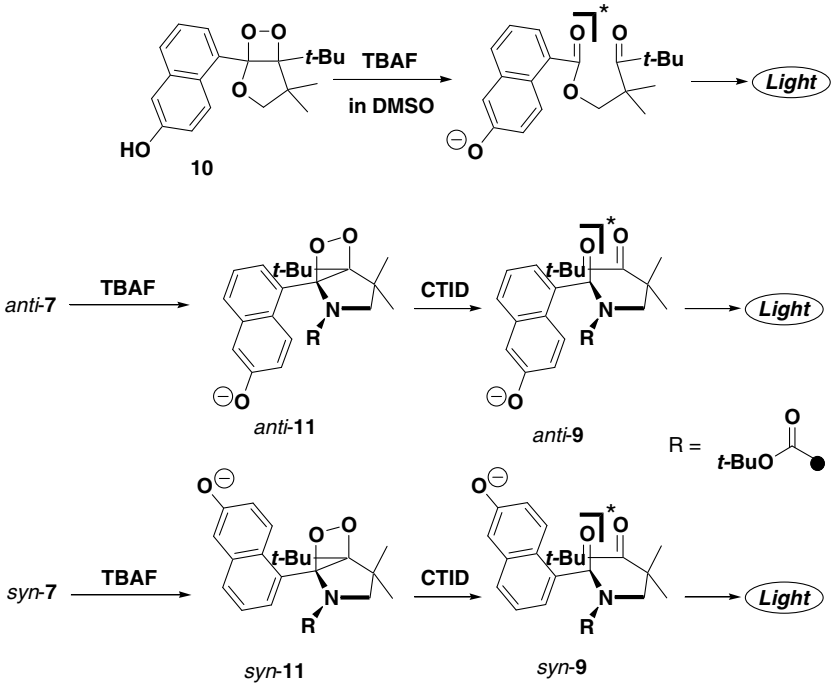


Figure 4. Chemiluminescence spectra of 3-hydroxyphenyldioxetane **1b**, 4-hydroxyphenyldioxetane **4**, and 6-hydroxynaphthalen-1-yl-dioxetanes *anti*-**7** and *syn*-**7**.

On the other hand, Φ_s for *anti*-**7** could not be reliably estimated since the chemiluminescence spectrum and fluorescence spectrum of authentic **9** deviated from each other to some extent. However, by using the Φ^{fl}s of authentic **9**, we formally estimated Φ_s for *anti*-**7** to be 0.23 in the DMSO system and 0.17 in the acetonitrile system. These formal Φ_ss are very close to the value of Φ_s reported for the CTID of related bicyclic dioxetane **10** bearing a 6-hydroxynaphthalen-1-yl group (0.23 in DMSO) (Scheme 3).[23] These estimations suggest that the marked difference in Φ^{CL} between *anti*-**7** and *syn*-**7** can be attributed to the difference in singlet-chemiexcitation efficiency.

As noted above, the chemiluminescence spectra of *anti*-**7** and *syn*-**7** did not coincide with each other, though both isomers **7** exclusively produced the same keto ester **8**. This discrepancy is likely due to the difference in stereochemistry between *de novo* keto imides **9**s formed from *anti*-**7** or *syn*-**7**. Thus, *de novo* **9**s, that is, *anti*-**9** and *syn*-**9**, may inherit the corresponding conformations from intermediary dioxetanes *anti*-**11** and *syn*-**11**, as illustrated in Scheme 3. This idea means that the features of singlet-chemiexcitation for *anti*-**11** should be different from those for *syn*-**11**. Tanaka, Tanaka and we (MM) will report elsewhere a theoretical elucidation of how the singlet-chemiexcitation process is affected by *syn*–*anti* conformational isomerism of dioxetane bearing an oxidoaryl group.[24]

The present findings should stimulate investigation of the mechanism of the singlet-chemiexcitation process for dioxetane-



Scheme 3.

based chemiluminescence as well as bioluminescence, and should provide new insight into the design of high-performance chemiluminescence compounds.

Acknowledgments

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14. *Selected data for* **1b**: Colorless amorphous solid; ^{1}H NMR (500 MHz, $CDCl_3$) (55:45 mixture of conformational isomers): δ_H 1.01 (s, 9H × 0.55), 1.01 (s, 9H × 0.45), 1.06–1.13 (m, 12H), 1.37 (s, 3H × 0.45), 1.40 (s, 3H × 0.55), 3.63 (d, J = 10.1 Hz, 1H), 4.06 (d, J = 10.1 Hz, 1H × 0.55), 4.07 (d, J = 10.1 Hz, 1H × 0.45), 6.25 (br s, 1H × 0.45), 6.45 (br s, 1H × 0.55), 6.79–6.88 (m, 2H), 7.15–7.27 (m, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 20.6, 25.7 and 25.7, 27.3 and 27.3, 27.7 and 27.8, 37.8 and 37.9, 43.0 and 43.1, 62.9 and 63.0, 81.2 and 81.4, 104.7 and 104.8, 106.2 and 106.5, 114.0 and 115.1, 115.5 and 116.2, 119.3 and 121.1, 128.7 and 128.8, 139.3 and 139.4, 154.5 and 154.9, 155.7 and 155.8 ppm; IR (KBr): ν 3401, 3006, 2979, 2931, 2892, 1706, 1674, 1604, 1592 cm^{-1}; Mass (m/z, %): 345 (M^+−32, 0.3), 278 (29), 264 (14), 220 (62), 192 (23), 121 (100), 93 (12), 57 (46), 56(20); HRMS (ESI): 400.2071, calcd for $C_{21}H_{31}NO_5Na$ [M+Na$^+$] 400.2100; Anal. Calcd for $C_{21}H_{31}NO_5$: C, 66.82; H, 8.28; N, 3.71; Found: C, 66.93; H, 8.36; N, 3.55.
15. A solution of **1b** in DMSO (1.0×10^{-5} mol dm^{-3}, 1 mL) was added to a solution of TBAF in DMSO (1.0×10^{-2} mol dm^{-3}, 2 mL).
16. Chemiluminescence efficiencies Φ^{CL}s were estimated based on the value for 3-(3-*tert*-butyldimethylsiloxy)phenyl-4-adamantylidene-4-methoxy-1,2-dioxetane.[17]
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19. *Selected data for anti-***7**: ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 0.69 (s, 9H), 0.88 (s, 9H), 1.26 (s, 3H), 1.60 (s, 3H), 3.95 (d, J = 10.5 Hz, 1H), 4.20 (d, J = 10.5 Hz, 1H), 5.27 (s, 1H), 7.07 (dd, J = 9.3 and 2.7 Hz, 1H), 7.19 (d, J = 2.7, 1H), 7.45 (dd, J = 8.3 and 7.6 Hz, 1H), 7.69 (d, J = 8.3 Hz, 1H), 7.97 (dd, J = 7.6 and 1.2 Hz, 1H), 8.42 (d, J = 9.3 Hz, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 22.0, 26.8, 26.9, 27.2, 37.9, 43.1, 63.1, 81.3, 104.3, 107.5, 111.1, 117.5, 125.3, 126.0, 126.3, 127.5, 128.5, 132.7, 135.5, 153.3, 154.3 ppm; IR (KBr): $\tilde{\nu}$ 3321, 3006, 2979, 2930, 2891, 1703, 1664, 1637, 1604 cm^{-1}; Mass (m/z, %): 427 (M^+, 10), 395 (4), 270 (94), 171 (100); HRMS (ESI): 450.2258, calcd for $C_{25}H_{33}NO_5Na$ [M + Na$^+$] 450.2256. Anal. Calcd for $C_{25}H_{33}NO_5$ + AcOEt (2.0 w/w %): C, 69.92; H, 7.81; N, 3.21; Found: C, 69.61; H, 7.74; N, 3.22.
20. *Crystal data for anti-***7**: $C_{25}H_{33}NO_5$ (M_r = 427.54), pale yellow granule, 0.25 × 0.15 × 0.10 mm, monoclinic, space group $P2_1/c$ (#14), a = 9.967(5) Å, b = 14.418(13) Å, c = 16.407(8) Å, β = 105.298(4)°, V = 2274.2(26) Å^3, Z = 4, ρ_{calcd} = 1.249 g cm^{-3}, T = 120 K, $F(000)$ = 920.00, reflections collected/unique 24965/5169 (R_{int} = 0.035), μ(MoKα) = 0.86 cm^{-1}. Final R indices R_1 = 0.067 [$I > 2\sigma(I)$], wR_2 = 0.184 (all data), GOF on F^2 = 0.879, and residual electron density 0.47/−0.52 e Å^{-3}.CCDC deposition number: 687258. *Crystal data for syn-***7**: $C_{25}H_{33}NO_5{\cdot}0.5(C_8H_{10})$ (M_r = 480.62), pale yellow prism, 0.25 × 0.10 × 0.10 mm, monoclinic, space group $P2_1/c$ (#14), a = 12.857(13) Å, b = 21.14(2) Å, c = 19.82(3) Å, β = 91.87(2)°, V = 5384.3(10) Å^3, Z = 8, ρ_{calcd} = 1.186 g cm^{-3}, T = 120 K, $F(000)$ = 2072.00, reflections collected/unique 57236/12215 (R_{int} = 0.095), μ(MoKα) = 0.80 cm^{-1}. Final R indices R_1 = 0.125 [$I > 2\sigma(I)$], wR_2 = 0.416 (all data), GOF on F^2 = 1.000, and residual electron density 0.31/−0.34 e Å^{-3}. CCDC deposition number: 687259.These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Center, 12 Union Road, Cambridge CB21EZ, UK; fax(+44)1223-336-033; or deposit@ccdc.cam.au.uk).
21. *syn-***7**: ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 0.81 (br s, 9H), 0.92 (s, 9H), 1.15 (s, 3H), 1.52 (s, 3H), 3.77 (d, J = 10.0 Hz, 1H), 4.18 (d, J = 10.0 Hz, 1H), 6.35–6.60 (m, 1H), 6.85–7.20 (m, 2H), 7.27–7.37 (m, 2H), 7.62 (d, J = 7.5 Hz, 1H), 8.79 (d, J = 9.5 Hz, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 21.3, 26.4, 27.4, 27.6, 38.0, 43.5, 63.1, 81.3, 108.0, 108.9, 109.9, 118.3, 124.1, 124.4, 127.8, 128.2, 129.5, 134.7, 135.8, 153.2, 154.6 ppm; IR (KBr): $\tilde{\nu}$ 3369, 2979, 2930, 1703, 1667, 1626, 1602 cm^{-1}; mass (m/z, %): 427 (M^+, 2), 395 (1), 270 (45), 171 (100); HRMS (ESI): 450.2257, calcd for $C_{25}H_{33}NO_5Na$ [M+Na$^+$] 450.2256. Anal. Calcd for $C_{26}H_{37}NO_4{\cdot}3/4\ C_6H_6$: C, 72.89; H, 7.78; N, 2.88; Found: C, 72.86; H, 7.86; N, 2.81.
22. A solution of *anti-***7** in DMSO (1.0×10^{-3} mol dm^{-3}, 1 mL) was added to a solution of TBAF in DMSO (1.0×10^{-1} mol dm^{-3}, 2 mL).
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