Check for updates

Three-component reaction of formyl-substituted donor–acceptor cyclopropanes, primary aromatic amines and 2-naphthol: access to cyclopropane fused 2-pyrrolidinone derivatives

Thangaraj Devaraj and Kannupal Srinivasan [ID] *

Formyl-substituted donor–acceptor cyclopropanes (DACs) participate in a three-component Betti reaction along with primary aromatic amines and 2-naphthol. The Betti bases initially formed in the transformation undergo spontaneous lactamization to yield cyclopropane-fused 2-pyrrolidine derivatives. The products are isolated as single diastereomers by simple trituration in moderate to good yields.
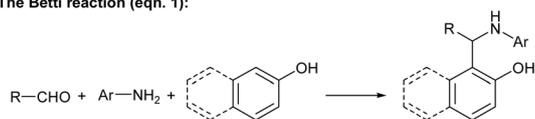
Introduction

Multi-component reactions (MCRs) are versatile tools for the construction of complex molecules from simple precursors with a spectacular efficiency.[1] Among various MCRs, the Mannich reaction is known for its flexibility as it allows several modifications in order to obtain a diverse array of products.[2] A three-component reaction of aldehydes, amines and phenols is an important modification among them and was introduced by Betti and co-workers (Scheme 1, eqn (1)).[3] The products of the reaction are called Betti bases, which serve as valuable synthetic intermediates for pharmaceutically relevant nitrogen heterocycles.[4] Donor–acceptor cyclopropanes (DACs) act as key building blocks for the access of various heterocyclic, carbocyclic and acyclic compounds.[5] Even though the reactivity of DACs having aryl donors and diester acceptors have been extensively investigated, that of similar cyclopropanes having an extra substituent such as formyl, aroyl or nitro has been only less explored.[6] In continuation of our interest in formyl-substituted DACs **1**,[7] we planned to investigate the Betti reaction of these cyclopropanes using primary aromatic amines **2** and 2-naphthol (**3**) (Scheme 1, eqn (2)). Pleasingly, the reaction afforded cyclopropane-fused 2-pyrrolidine derivatives **4**, instead of regular Betti base products. It may be noted that 2-pyrrolidine core is widespread among medicinally active natural and synthetic products and hence many methods have been developed for the synthesis of pyrrolidine derivatives.[8]
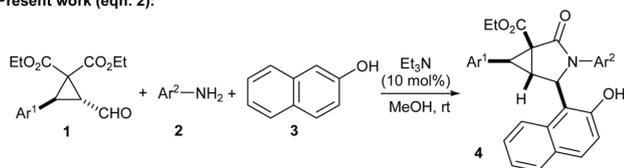
Results and discussion

We began the study by reacting formyl-substituted DAC **1a** with aniline (**2a**) and 2-naphthol (**3**) in MeOH at room temperature without using any base catalyst. Unfortunately, the reaction stopped at the imine stage and further addition of 2-naphthol did not take place even after 24 h (Table 1, entry 1). Next, we used a catalytic amount (10 mol%) of triethylamine to initiate the reaction. Pleasingly, the reaction smoothly took place at room temperature (16 h) and yielded cyclopropane-fused 2-pyrrolidine derivative **4a** in 83% yield (entry 2) (the structure of **4a** was confirmed by X-ray analysis[9]). When the amount of triethylamine was reduced to 5 mol%, the yield of **4a** decreased to 54% (entry 3). At the same time, the yield of **4a** did not change significantly when 20 mol% of triethylamine was used (entry 4). We also employed different solvents in the transformation (entries 5–9). But, **4a** was formed only in low yields in ethanol, dichloromethane, chloroform and acetonitrile (entries 5–8) and the reaction stops at the imine stage in THF, toluene and DMF (entry 9). We also examined other tertiary amine bases such as DBU and DABCO; but, the reactions did not give the expected product **4a** (entries 10 and 11). Shahrisa and co-workers have reported that tertiary amines having hydrogen bond donors catalyze the Betti reaction efficiently.[10] So, we used *N,N′*-
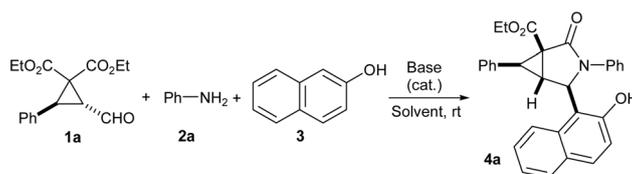

Scheme 1 The Betti reaction and the present work.

School of Chemistry, Bharathidasan University, Tiruchirappalli-620024, Tamil Nadu, India. E-mail: srinivasank@bdu.ac.in; Tel: +91-431-2407053

Table 1 Optimisation of reaction conditions[a]

Entry	Reaction conditions	Yield of **4a** (%)[b]
1	None, MeOH, 24 h	—[c]
2	Triethylamine (10 mol%), MeOH, 16 h	83
3	Triethylamine (5 mol%), MeOH, 16 h	54
4	Triethylamine (20 mol%), MeOH, 16 h	82
5	Triethylamine (10 mol%), EtOH, 18 h	59
6	Triethylamine (10 mol%), DCM, 8 h	62
7	Triethylamine (10 mol%), CHCl$_3$, 12 h	64
8	Triethylamine (10 mol%), MeCN, 12 h	60
9	Triethylamine (10 mol%), THF, toluene or DMF, 24 h	—[c]
10	DBU (10 mol%), MeOH, 48 h	—[d]
11	DABCO (10 mol%), MeOH, 48 h	—[d]
12	N,N'-dimethylethanolamine (10 mol%), MeOH, 18 h	62
13	Diethanolamine (10 mol%), MeOH, 23 h	30
14	Triethanolamine (10 mol%), MeOH, 72 h	24
15	K$_2$CO$_3$ (10 mol%), MeOH, 60 h	—[c]

[a] The reaction was carried out with **1a** (1.0 mmol), **2a** (1.3 mmol), **3** (1.3 mmol), base (x mol%) and solvent (1 mL). [b] Isolated yield. [c] The reaction stopped at the imine stage. [d] Product **4a** was not found.

dimethylethanolamine as a catalyst for the transformation (entry 12). Nevertheless, the yield of **4a** was only 62% and also the reaction time increased to 18 h. We also tested the suitability of similar catalysts such as diethanolamine and triethanolamine; however, the yields of **4a** were only 30% (23 h) and 24% (72 h), respectively with those catalysts (entries 13 and 14). When an inorganic base, K$_2$CO$_3$ was used, the reaction stopped at the imine stage (entry 15). So, we selected stirring a mixture DAC **1a** with aniline (**2a**) and 2-naphthol (**3**) in the presence of triethylamine (10 mol%) in MeOH at room temperature as the optimal condition for the transformation.

With the optimized reaction condition in hand, we set out to investigate the scope of the transformation and the results are summarized in Table 2. Initially, we reacted DACs **1a–e** having different electron donating and withdrawing substituents on the aryl ring with aniline (**2a**) and 2-naphthol (**3**) under the optimized conditions (entries 1–5). The results reveal that the electronic nature of the aryl ring is strongly influencing the outcome of the transformations. Especially, when a methoxy substituent was present on the aryl ring at 2- or 4-positions, the yields of the respective 2-pyrrolidine derivatives **4c** and **4d** were poor (entries 3 and 4) and when a nitro group is present, the expected product did not form (entry 5). Next, we reacted DACs **1a–d** and **1f** with toluidine (**2b**) and anisidine (**2c**) and obtained the corresponding 2-pyrrolidine derivatives **4f–o** in a similar trend of yields (entries 6–15). The presence of a halogen substituent is not only tolerated on the aryl ring of the cyclopropane (entries 10 and 15), but also on the aryl ring of the

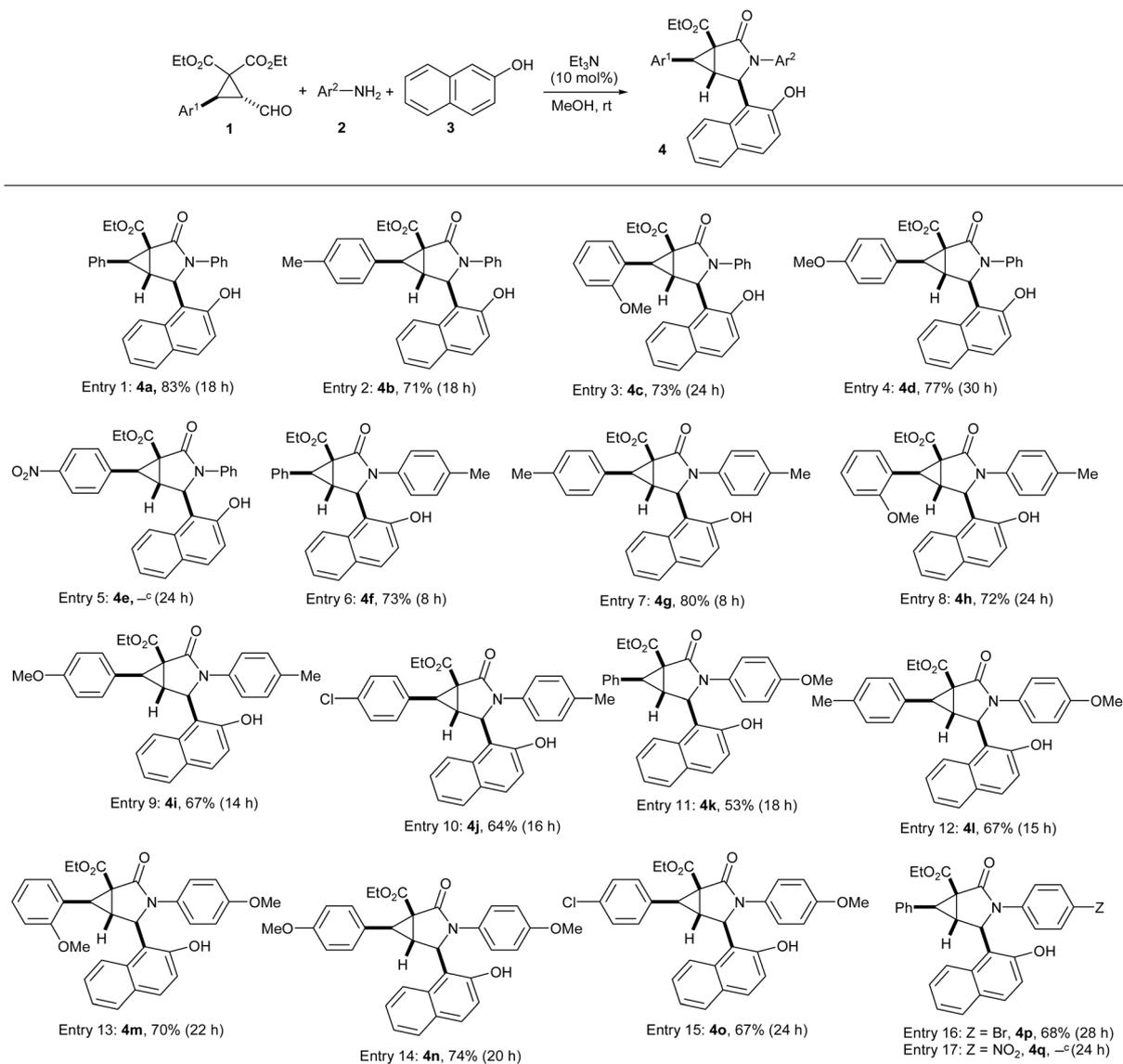amine (entry 16). However, 4-nitroaniline was not compatible in the transformation (entry 17).

The reaction was very sensitive with respect to the phenolic component and only 2-naphthol was found to be an apt substrate. Others such as phenol, m-cresol, 4-methoxyphenol, 4-chlorophenol, 4-nitrophenol, 1-naphthol, 2,3-dihydroxynaphthalene, 2,6-dihydroxynaphthalene, methyl-3-hydroxy-2-naphthoate and 6-bromo-2-naphthol did not yield the expected products.

During the course of the study, we were pleased to observe that aminopyridines could be used in the place of anilines in the transformations. Accordingly, when DAC **1a** was reacted with 2-aminopyridine (**5a**)/4-methyl-2-aminopyridine (**5b**) and 2-naphthol in the presence of triethylamine in MeOH, the corresponding cyclopropane-fused 2-pyrrolidine derivatives **6a** and **6b** in 74 and 78% yields, respectively (Scheme 2).
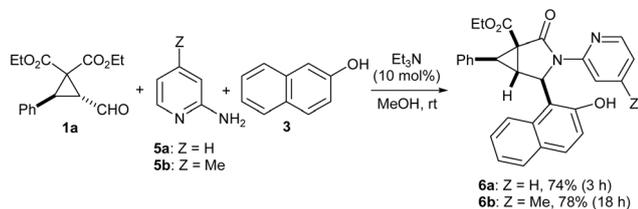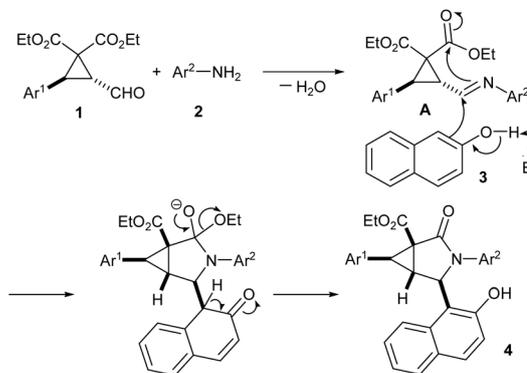
A plausible mechanism for the transformation is shown in Scheme 3. Initially, formyl-substituted DACs **1** undergo condensation with anilines **2** to form imines **A**. Subsequent deprotonation of 2-naphthol (**3**) by base (triethylamine) gives naphthoxide which acts as C-nucleophile and attacks imine **A**. The resulting negatively charged nitrogen attacks one of the ester groups intramolecularly, leading the formation of cyclised products **4** with the loss of an ethoxy group.

We have also investigated further synthetic transformations of the products formed in the present study (Scheme 4). Accordingly, when **4a** was treated with potassium hydroxide and dimethyl sulphate in THF/MeOH under reflux conditions, it undergoes O-methylation as well as decarbethoxylation to give

Table 2 The scope of the transformation[a,b]

Entry 1: **4a**, 83% (18 h)

Entry 2: **4b**, 71% (18 h)

Entry 3: **4c**, 73% (24 h)

Entry 4: **4d**, 77% (30 h)

Entry 5: **4e**, −[c] (24 h)

Entry 6: **4f**, 73% (8 h)

Entry 7: **4g**, 80% (8 h)

Entry 8: **4h**, 72% (24 h)

Entry 9: **4i**, 67% (14 h)

Entry 10: **4j**, 64% (16 h)

Entry 11: **4k**, 53% (18 h)

Entry 12: **4l**, 67% (15 h)

Entry 13: **4m**, 70% (22 h)

Entry 14: **4n**, 74% (20 h)

Entry 15: **4o**, 67% (24 h)

Entry 16: Z = Br, **4p**, 68% (28 h)
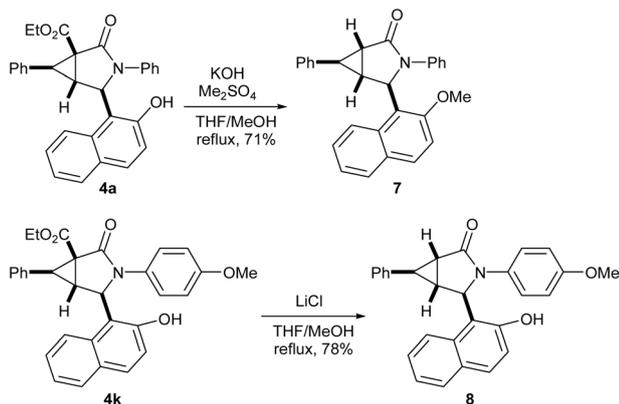Entry 17: Z = NO$_2$, **4q**, −[c] (24 h)

[a] The reaction was carried out with **1** (1.0 mmol), **2** (1.3 mmol), **3** (1.3 mmol), Et$_3$N (10 mol%) and MeOH (1 mL). [b] Isolated yield. [c] Not found.

Scheme 2 Reaction of DAC **2a** with 2-aminopyridines and 2-naphthol.

product **7** in 71% yield. Similarly, when **4k** was subjected to Krapcho decarbethoxylation using lithium chloride in THF/MeOH under reflux conditions, product **8** was produced in 78% yield.

Scheme 3 Mechanism of the transformation.

Scheme 4 Further synthetic transformations of the 2-pyrrolidinone derivatives.

Conclusions

In summary, we have developed a convenient procedure for the synthesis of cyclopropane-fused 2-pyrrolidine derivatives from the Betti reaction of formyl-substituted DACs with primary aromatic amines and 2-naphthol. The reaction did not stop at the usual Betti base (amine) stage and further lactamization took place concurrently to give 2-pyrrolidinone derivatives as products. The procedure is operationally simple and the products were isolated as single diastereomers in moderate to good yields without any column chromatographic purification.

Experimental section

General remarks

Melting points were determined by the open capillary tube method and are uncorrected. The ^{1}H and ^{13}C NMR spectra were recorded on a 400 MHz NMR spectrometer. High-resolution mass spectra (SI) were recorded on a Q-TOF mass spectrometer. X-ray crystallographic data were collected on a CCD diffractometer using graphite-monochromated Mo Kα radiation. Thin layer chromatography (TLC) was performed on pre-coated alumina sheets and detected under UV light. Silica gel (100–200 mesh) was used for column chromatography. Cyclopropanes **1a–f** were prepared as per the reported procedure[7] and all are known compounds.

General procedure for the synthesis of cyclopropane-fused 2-pyrrolidine derivatives 4a–d, 4f–p and 6a–b

To a solution of cyclopropane aldehyde **1** (1.0 mmol) in methanol (1 mL) in a RB flask fitted with a guard tube were added aniline **2** (121 mg, 1.3 mmol) followed by 2-naphthol **3** (187 mg, 1.3 mmol) and triethylamine (14 µL, 10 mol%) and the reaction mixture was stirred at rt for 3–30 h. After completion of the reaction, the solid precipitated was filtered and titurated with methanol repeatedly to obtain the pure product.

Ethyl 4-(2-hydroxynaphthalen-1-yl)-2-oxo-3,6-diphenyl-3-azabicyclo [3.1.0] hexane-1-carboxylate (4a)

White solid. Yield: 384 mg (83%). R_f = 0.40 (hexane/EtOAc, 1 : 9 v/v). Mp: 256–258 °C; ^{1}H NMR (400 MHz, CDCl$_3$): δ 8.10 (d, J = 8.8 Hz, 2H), 7.83 (d, J = 8.0 Hz, 1H), 7.74 (d, J = 8.8 Hz, 2H), 7.64–7.56 (m, 1H), 7.46 (d, J = 8.8 Hz, 2H), 7.39–7.29 (m, 5H), 7.13 (d, J = 8.8 Hz, 3H), 6.09 (s, 1H), 3.83–3.79 (m, 2H), 3.65–3.61 (m, 1H), 3.18 (s, 2H), 0.71 (t, J = 7.0 Hz, 3H) ppm. ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$): δ171.8, 165.2, 154.9, 137.0, 133.2, 132.4, 131.8, 130.6, 129.3, 129.0, 128.3, 127.4, 124.4, 123.0, 120.2, 119.7, 114.1, 61.0, 58.2, 42.7, 39.5, 28.6, 13.7 ppm. HRMS (SI–TOF) m/z: [M + H]$^+$ calcd for C$_{30}$H$_{26}$NO$_4$, 464.1856; found: 464.1878.

Ethyl 4-(2-hydroxynaphthalen-1-yl)-2-oxo-3-phenyl-6-(p-tolyl)-3-azabicyclo [3.1.0] hexane-1-carboxylate (4b)

White solid. Yield: 340 mg (71%). R_f = 0.23 (hexane/EtOAc, 1 : 9 v/v). Mp: 260–262 °C; ^{1}H NMR (400 MHz, CDCl$_3$): δ 8.15–8.06 (m, 1H), 7.80 (d, J = 8.0 Hz, 1H), 7.70 (d, J = 8.8 Hz, 1H), 7.55 (t, J = 7.6 Hz, 1H), 7.47 (d, J = 8.8 Hz, 2H), 7.42 (d, J = 8.0 Hz, 2H), 7.36 (t, J = 7.4 Hz, 1H), 7.24 (d, J = 7.6 Hz, 3H), 7.12 (d, J = 8.0 Hz, 1H), 7.03 (t, J = 7.8 Hz, 1H), 6.94 (t, J = 7.2 Hz, 1H), 6.12 (s, 1H), 3.89–3.82 (m, 2H), 3.66–3.60 (m, 1H), 3.15 (s, 2H), 2.34 (s, 3H), 0.75 (t, J = 7.0 Hz, 3H) ppm. ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$): δ 171.8, 165.3, 155.0, 138.0, 137.3, 132.5, 130.3, 130.2, 129.1, 128.92, 128.9, 128.7, 127.1, 125.4, 123.0, 122.7, 120.5, 119.9, 114.7, 60.9, 58.3, 42.9, 39.3, 28.5, 21.1, 13.8 ppm. HRMS (SI–TOF) m/z: [M + H]$^+$ calcd for C$_{31}$H$_{28}$NO$_4$, 478.2013; found: 478.2031.

Ethyl 4-(2-hydroxynaphthalen-1-yl)-6-(2-methoxyphenyl)-2-oxo-3-phenyl-3-azabicyclo [3.1.0] hexane-1-carboxylate (4c)

White solid. Yield: 360 mg (73%). R_f = 0.40 (hexane/EtOAc, 1 : 9 v/v). Mp: 261–262 °C; ^{1}H NMR (400 MHz, CDCl$_3$): δ 8.14 (d, J = 8.4 Hz, 1H), 7.79 (d, J = 8.0 Hz, 1H), 7.68 (d, J = 8.8, 1H), 7.56 (t, J = 7.4 Hz, 2H), 7.45–7.34 (m, 3H), 7.26 (d, J = 7.6 Hz, 2H), 7.20 (d, J = 7.2 Hz, 1H), 7.02–6.98 (m, 2H), 6.94–6.86 (m, 2H), 6.13 (s, 1H), 3.90 (s, 3H), 3.76–3.68 (m, 2H), 3.21 (d, J = 5.6 Hz, 1H), 3.12 (d, J = 6.0 Hz, 2H), 0.73 (t, J = 7.2 Hz, 3H) ppm. ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$): δ 171.8, 166.0, 158.8, 154.9, 138.1, 132.6, 130.2, 129.4, 129.1, 128.8, 128.6, 127.0, 125.3, 123.2, 120.6, 119.9, 114.9, 110.1, 60.6, 58.1, 55.6, 41.5, 35.4, 29.3, 13.7 ppm. HRMS (SI–TOF) m/z: [M + H]$^+$ calcd for C$_{31}$H$_{28}$NO$_5$, 494.1962; found: 494.1985.

Ethyl 4-(2-hydroxynaphthalen-1-yl)-6-(4-methoxyphenyl)-2-oxo-3-phenyl-3-azabicyclo [3.1.0] hexane-1-carboxylate (4d)

White solid. Yield: 381 mg (77%). R_f = 0.29 (hexane/EtOAc, 1 : 9 v/v). Mp: 218–220 °C; ^{1}H NMR (400 MHz, CDCl$_3$): δ 8.15 (d, J = 8.4 Hz, 1H), 7.79 (d, J = 8.0 Hz, 1H), 7.69 (d, J = 8.8 Hz, 1H), 7.58–7.54 (m, 1H), 7.46–7.42 (m, 2H), 7.36 (t, J = 7.4 Hz, 2H), 7.29 (d, J = 10.8 Hz, 1H), 7.25–7.19 (m, 2H), 7.02–6.99 (m, 2H), 6.94–6.88 (m, 2H), 6.14 (s, 1H), 3.90 (s, 3H), 3.76–3.68 (m, 2H), 3.21 (d, J = 5.6 Hz, 2H), 3.12 (d, J = 6.0 Hz, 1H), 0.75 (t, J = 7.0 Hz, 3H) ppm. ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$): δ 171.7,

165.9, 158.8, 154.8, 138.2, 132.6, 130.1, 129.4, 129.1, 128.8, 128.6, 127.0, 125.2, 123.0, 122.7, 122.3, 120.6, 119.9, 115.0, 110.2, 60.6, 58.1, 55.6, 41.5, 35.3, 29.2, 13.7 ppm. HRMS (SI–TOF) m/z: $[M + H]^+$ calcd for $C_{31}H_{28}NO_5$, 494.1962; found: 494.1988.

Ethyl-4-(2-hydroxynaphthalen-1-yl)-2-oxo-6-phenyl-3-(*p*-tolyl)-3-azabicyclo [3.1.0] hexane-1-carboxylate (4f)

White solid. Yield: 349 mg (73%). R_f = 0.40 (hexane/EtOAc, 1 : 9 v/v). Mp: 278–280 °C; ^{1}H NMR (400 MHz, CDCl$_3$): δ 8.09 (d, J = 8.4 Hz, 1H), 7.80 (d, J = 8.0 Hz, 1H), 7.71 (d, J = 8.8 Hz, 1H), 7.54 (t, J = 7.6 Hz, 1H), 7.42 (d, J = 8.8 Hz, 2H), 7.36 (d, J = 7.2 Hz, 3H), 7.33–7.26 (m, 4H), 6.83 (d, J = 8.0 Hz, 2H), 6.07 (s, 1H), 3.91–3.84 (m, 2H), 3.73–3.65 (m, 1H), 3.16 (s, 2H), 2.12 (s, 3H), 0.75 (t, J = 7.2 Hz, 3H) ppm. ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$): δ 171.3, 165.3, 154.7, 135.3, 135.1, 133.6, 132.6, 130.2, 129.3, 129.1, 129.0, 128.8, 128.2, 127.6, 127.1, 123.2, 122.8, 120.6, 119.8, 115.0, 60.9, 58.3, 42.7, 39.3, 28.6, 20.8, 13.7 ppm. HRMS (SI–TOF) m/z: $[M + H]^+$ calcd for $C_{31}H_{28}NO_4$, 478.2013; found: 478.2026.

Ethyl 4-(2-hydroxynaphthalen-1-yl)-2-oxo-3,6-di-*p*-tolyl-3-azabicyclo [3.1.0] hexane-1-carboxylate (4g)

White solid. Yield: 392 mg (80%). R_f = 0.50 (hexane/EtOAc, 1 : 9 v/v). Mp: 278–280 °C; ^{1}H NMR (400 MHz, CDCl$_3$): δ 8.19 (s, 1H), 8.09 (d, J = 8.4 Hz, 1H), 7.79 (d, J = 8.0 Hz, 1H), 7.19 (d, J = 8.8 Hz, 2H), 7.55–7.48 (m, 1H), 7.35–7.24 (m, 4H), 7.12 (d, J = 7.6 Hz, 2H), 6.81 (d, J = 8.0 Hz, 2H), 6.07 (s, 1H), 3.91–3.85 (m, 2H), 3.67–3.61 (m, 1H), 3.14 (s, 2H), 2.34 (s, 3H), 2.11 (s, 3H), 0.77 (t, J = 7.0 Hz, 3H) ppm. ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$): δ 171.9, 165.4, 155.1, 137.3, 135.1, 132.6, 130.4, 129.3, 129.0, 128.9, 127.0, 123.3, 122.6, 120.6, 120.0, 114.6, 60.9, 58.4, 42.8, 39.4, 28.6, 21.1, 20.8, 13.8 ppm. HRMS (SI–TOF) m/z: $[M + H]^+$ calcd for $C_{32}H_{30}NO_4$, 492.2169; found: 492.2177.

Ethyl 4-(2-hydroxynaphthalen-1-yl)-6-(2-methoxyphenyl)-2-oxo-3-(*p*-tolyl)-3-azabicyclo [3.1.0] hexane-1-carboxylate (4h)

White solid. Yield: 365 mg (72%). R_f = 0.19 (hexane/EtOAc, 1 : 9 v/v). Mp: 262–264 °C; ^{1}H NMR (400 MHz, CDCl$_3$): δ 8.25 (s, 1H), 8.12 (d, J = 8.4 Hz, 1H), 7.77 (d, J = 8.0 Hz, 1H), 7.64 (d, J = 8.8 Hz, 1H), 7.56–7.45 (m, 2H), 7.34–7.20 (m, 5H), 6.89 (d, J = 8.0 Hz, 1H), 6.76 (d, J = 8.0 Hz, 2H), 6.10 (s, 1H), 3.90 (s, 3H), 3.73–3.67 (m, 2H), 3.34–3.21 (m, 2H), 3.13 (d, J = 5.6 Hz, 1H), 2.09 (s, 3H), 0.74 (t, J = 7.0 Hz, 3H) ppm. ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$): δ 172.0, 166.1, 158.8, 155.2, 135.4, 134.9, 132.7, 130.0, 129.5, 129.3, 129.1, 128.8, 128.6, 126.9, 123.4, 122.5, 120.6, 120.1, 119.9, 114.8, 110.1, 60.6, 58.3, 55.6, 41.4, 35.5, 29.4, 20.8, 13.7 ppm. HRMS (SI–TOF) m/z: $[M + H]^+$ calcd for $C_{32}H_{30}NO_5$, 508.2118; found: 508.2117.

Ethyl 4-(2-hydroxynaphthalen-1-yl)-6-(4-methoxyphenyl)-2-oxo-3-(*p*-tolyl)-3-azabicyclo [3.1.0] hexane-1-carboxylate (4i)

White solid. Yield: 340 mg (67%). R_f = 0.38 (hexane/EtOAc, 1 : 9 v/v). Mp: 268–270 °C; ^{1}H NMR (400 MHz, CDCl$_3$): δ 8.12 (d, J = 9.2 Hz, 2H), 7.77 (d, J = 8.0 Hz, 1H), 7.65 (d, J = 8.8 Hz, 1H), 7.53–7.43 (m, 2H), 7.34–7.26 (m, 4H), 6.91 (d, J = 7.2 Hz, 2H), 6.77 (d, J = 8.0 Hz, 2H), 6.10 (s, 1H), 3.90 (s, 3H), 3.75–3.69 (m, 2H), 3.25–3.17 (m, 1H), 3.13 (d, J = 5.6 Hz, 2H), 2.10 (s, 3H), 0.74 (t, J = 7.0 Hz, 3H) ppm. ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$): δ 171.4, 165.5, 159.1, 154.8, 135.9, 135.1, 132.9, 130.2, 129.3, 129.1, 127.1, 125.4, 123.7, 123.1, 122.7, 120.6, 119.8, 117.8, 113.6, 109.5, 61.0, 58.3, 55.3, 42.8, 39.1, 28.3, 20.8, 13.8 ppm. HRMS (SI–TOF) m/z: $[M + H]^+$ calcd for $C_{32}H_{30}NO_5$, 508.2118; found: 508.2125.

Ethyl 6-(4-chlorophenyl)-4-(2-hydroxynaphthalen-1-yl)-2-oxo-3-(*p*-tolyl)-3-azabicyclo [3.1.0] hexane-1-carboxylate (4j)

White solid. Yield: 330 mg (64%). R_f = 0.31 (hexane/EtOAc, 1 : 9 v/v). Mp: 284–286 °C; ^{1}H NMR (400 MHz, CDCl$_3$): δ 8.08 (d, J = 8.8 Hz, 2H), 7.79 (d, J = 8.0 Hz, 1H), 7.69 (d, J = 8.8 Hz, 1H), 7.53 (t, J = 7.4 Hz, 1H), 7.46 (d, J = 8.4 Hz, 1H), 7.37–7.23 (m, 5H), 8.81 (d, J = 7.6 Hz, 3H), 6.07 (s, 1H), 4.01–3.87 (m, 2H), 3.67 (d, J = 7.6 Hz, 1H), 3.12 (s, 2H), 2.11 (s, 3H), 0.78 (t, J = 6.6 Hz, 3H) ppm. ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$): δ 171.4, 165.2, 155.1, 135.3, 133.5, 132.5, 132.1, 130.4, 130.3, 129.4, 129.1, 128.7, 128.3, 127.1, 123.3, 122.7, 120.9, 119.8, 114.5, 61.1, 58.3, 42.6, 38.6, 28.9, 20.7, 13.8 ppm. HRMS (SI–TOF) m/z: $[M + H]^+$ calcd for $C_{31}H_{27}ClNO_4$, 512.1623; found: 512.1629.

Ethyl 4-(2-hydroxynaphthalen-1-yl)-3-(4-methoxyphenyl)-2-oxo-6-phenyl-3-azabicyclo [3.1.0] hexane-1-carboxylate (4k)

White solid. Yield: 260 mg (53%). R_f = 0.50 (hexane/EtOAc, 1 : 9 v/v). Mp: 272–274 °C; ^{1}H NMR (400 MHz, CDCl$_3$): δ 8.10 (d, J = 8.8 Hz, 2H), 7.83 (d, J = 8.0 Hz, 2H), 7.74 (d, J = 8.8 Hz, 2H), 7.60–7.56 (m, 2H), 7.43–7.29 (m, 4H), 7.14 (d, J = 8.8 Hz, 3H), 6.09 (s, 1H), 3.86–3.81 (m, 1H), 3.69–3.64 (m, 2H), 3.53 (s, 3H), 3.17 (s, 2H), 0.74 (t, J = 7.0 Hz, 3H) ppm. ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$): δ 171.6, 165.2, 154.8, 137.1, 133.2, 132.4, 131.8, 130.6, 129.3, 129.0, 128.8, 128.2, 127.7, 127.4, 124.4, 123.0, 120.3, 119.6, 118.6, 114.3, 61.0, 58.1, 50.9, 42.7, 39.4, 28.6, 13.7 ppm. HRMS (ESI–TOF) m/z: $[M + H]^+$ calcd for $C_{31}H_{28}NO_5$, 494.1962; found: 494.1970.

Ethyl 4-(2-hydroxynaphthalen-1-yl)-3-(4-methoxyphenyl)-2-oxo-6-(*p*-tolyl)-3-azabicyclo [3.1.0] hexane-1-carboxylate (4l)

White solid. Yield: 338 mg (67%). R_f = 0.47 (hexane/EtOAc, 1 : 9 v/v). Mp: 288–290 °C; ^{1}H NMR (400 MHz, CDCl$_3$): δ 8.06 (d, J = 8.8 Hz, 1H), 7.79 (d, J = 8.0 Hz, 1H), 7.70 (d, J = 8.8 Hz, 1H), 7.51 (t, J = 7.4 Hz, 1H), 7.41 (d, J = 8.8 Hz, 1H), 7.30–7.24 (m, 4H), 7.12 (d, J = 7.6 Hz, 3H), 6.54 (d, J = 8.8 Hz, 2H), 6.01 (s, 1H), 3.96–3.90 (m, 1H), 3.77–3.71 (m, 2H), 3.56 (s, 3H), 3.14 (s, 2H), 2.34 (s, 3H), 0.82 (t, J = 7.0 Hz, 3H) ppm. ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$): δ 171.6, 165.6, 157.3, 154.9, 137.3, 132.7, 130.4, 130.2, 129.1, 128.92, 128.87, 128.7, 127.0, 125.2, 122.7, 120.6, 119.8, 114.9, 113.9, 113.8, 61.0, 58.6, 55.2, 42.6, 39.5, 28.8, 21.1, 13.8 ppm. HRMS (SI–TOF) m/z: $[M + H]^+$ calcd for $C_{32}H_{30}NO_5$, 508.2118; found: 508.2143.

Ethyl 4-(2-hydroxynaphthalen-1-yl)-6-(2-methoxyphenyl)-3-(4-methoxyphenyl)-2-oxo-3-azabicyclo [3.1.0] hexane-1-carboxylate (4m)

White solid. Yield: 368 mg (70%). R_f = 0.30 (hexane/EtOAc, 1 : 9 v/v). Mp: 248–250 °C; ^{1}H NMR (400 MHz, CDCl$_3$): δ 8.37(s, 1H), 8.08 (d, J = 8.8 Hz, 1H), 7.76 (d, J = 8.0 Hz, 1H), 7.64 (d, J = 8.8 Hz, 1H), 7.49 (d, J = 8.8 Hz, 2H), 7.32–7.21 (m, 5H), 6.40 (d, J = 8.0 Hz, 1H), 6.46 (d, J = 8.8 Hz, 2H), 6.04 (s, 1H), 3.91 (s, 3H), 3.78–3.73 (m, 2H), 3.49 (s, 3H), 3.34–3.23 (m, 2H), 3.14 (d, J = 5.6 Hz, 1H), 0.75 (t, J = 7.0 Hz, 3H) ppm. ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$): δ 172.2, 166.2, 158.8, 157.2, 155.3, 132.7, 130.7, 130.1, 129.6, 129.1, 128.8, 126.8, 125.5, 122.5, 122.4, 120.6, 120.0, 119.9, 114.7, 113.9, 110.1, 60.5, 58.6, 55.6, 55.1, 41.2, 35.7, 29.5, 13.7 ppm. HRMS (SI–TOF) m/z: [M + H]$^+$ calcd for C$_{32}$H$_{30}$NO$_6$, 524.2068; found: 524.2091.

Ethyl 4-(2-hydroxynaphthalen-1-yl)-3,6-bis(4-methoxyphenyl)-2-oxo-3-azabicyclo [3.1.0] hexane-1-carboxylate (4n)

White solid. Yield: 386 mg (74%). R_f = 0.25 (hexane/EtOAc, 1 : 9 v/v). Mp: 266–268 °C; ^{1}H NMR (400 MHz, CDCl$_3$): δ 8.05 (d, J = 8.8 Hz, 1H), 7.79 (d, J = 8.0 Hz, 1H), 7.70 (d, J = 8.8 Hz, 1H), 7.53–7.49 (m, 1H), 7.40–7.29 (m, 1H), 7.26 (d, J = 9.2 Hz, 5H), 6.85 (d, J = 8.4 Hz, 2H), 6.54 (d, J = 6.8 Hz, 2H), 6.00 (s, 1H), 3.94–3.85 (m, 2H), 3.81 (s, 3H), 3.67 (d, = 8.0 Hz, 1H), 3.56 (s, 3H), 3.12 (s, 1H), 0.83 (t, J = 6.2 Hz, 3H) ppm. ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$): δ 171.5, 165.6, 159.1, 157.3, 154.8, 132.7, 130.7, 130.2, 130.1, 129.0, 128.7, 127.0, 125.4, 125.3, 122.7, 120.6, 119.7, 114.9, 114.0, 113.8, 113.6, 61.0, 58.6, 55.2, 55.1, 42.6, 39.2, 28.9, 13.8 ppm. HRMS (SI–TOF) m/z: [M + H]$^+$ calcd for C$_{32}$H$_{30}$NO$_6$, 524.2068; found: 524.2090.

Ethyl 6-(4-chlorophenyl)-4-(2-hydroxynaphthalen-1-yl)-3-(4-methoxy-phenyl)-2-oxo-3-azabicyclo [3.1.0] hexane-1-carboxylate (4o)

White solid. Yield: 352 mg (67%). R_f = 0.45 (hexane/EtOAc, 1 : 9 v/v). Mp: 298–300 °C; ^{1}H NMR (400 MHz, CDCl$_3$): δ 8.04 (d, J = 8.8 Hz, 2H), 7.79 (d, J = 8.0 Hz, 2H), 7.70 (d, J = 8.8 Hz, 2H), 7.53–7.49 (m, 1H), 7.43 (d, J = 8.8 Hz, 1H), 7.35 (d, J = 7.6 Hz, 1H), 7.24 (d, J = 8.4 Hz, 3H), 6.52 (d, J = 8.4 Hz, 2H), 6.02 (s, 1H), 3.97–3.89 (m, 1H), 3.76–3.69 (m, 2H), 3.55 (s, 3H), 3.14 (s, 2H), 0.81 (t, J = 7.2 Hz, 3H) ppm. ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$): δ 171.3, 165.3, 157.4, 155.0, 133.5, 132.6, 130.4, 130.3, 129.1, 128.4, 127.0, 125.3, 122.8, 120.5, 119.8, 114.0, 61.1, 58.5, 55.1, 42.5, 38.8, 28.9, 13.8 ppm. HRMS (SI–TOF) m/z: [M + H]$^+$ calcd for C$_{31}$H$_{27}$ClNO$_5$, 528.1572; found: 528.1587.

Ethyl 3-(4-bromophenyl)-4-(2-hydroxynaphthalen-1-yl)-2-oxo-6-phenyl-3-azabicyclo [3.1.0] hexane-1-carboxylate (4p)

White solid. Yield: 366 mg (68%). R_f = 0.42 (hexane/EtOAc, 1 : 9 v/v). Mp: 258–260 °C; ^{1}H NMR (400 MHz, CDCl$_3$): δ 8.11 (d, J = 8.8 Hz, 1H), 7.83 (d, J = 8.0 Hz, 1H), 7.74 (d, J = 9.2 Hz, 2H), 7.59–7.56 (m, 1H), 7.44–7.30 (m, 8H), 7.14 (d, J = 8.8 Hz, 2H), 6.08 (s, 1H), 3.85–3.80 (m, 2H), 3.68–3.64 (m, 1H), 3.52 (s, 1H), 3.17 (s, 1H), 0.73 (t, J = 7.2 Hz, 3H) ppm. ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$): δ 171.6, 165.2, 154.8, 137.1, 133.2, 132.4, 131.8, 130.1, 129.3, 129.0, 128.8, 128.2, 127.7, 127.4, 124.4, 123.0, 120.3, 119.7, 118.6, 114.3, 61.0, 58.1, 42.7, 39.4, 28.6, 13.7 ppm. HRMS (SI–TOF) m/z: [M + H]$^+$ calcd for C$_{30}$H$_{25}$BrNO$_4$, 542.0961; found: 542.0968.

Ethyl 4-(2-hydroxynaphthalen-1-yl)-2-oxo-6-phenyl-3-(pyridin-2-yl)-3-azabicyclo [3.1.0] hexane-1-carboxylate (6a)

White solid. Yield: 344 mg (74%). R_f = 0.50 (hexane/EtOAc, 1 : 9 v/v). Mp: 240–242 °C; ^{1}H NMR (400 MHz, CDCl$_3$): δ 8.61 (d, J = 8.8 Hz, 2H). 8.34 (d, J = 4.8 Hz, 2H), 8.04 (d, J = 8.4 Hz, 2H), 7.84–7.77 (m, 3H), 7.41–7.27 (m, 4H), 7.12 (t, J = 6.0 Hz, 2H), 6.32 (s, 1H), 4.13–4.04 (m, 2H), 3.34 (d, J = 5.2 Hz, 1H), 3.16 (d, J = 5.2 Hz, 2H), 0.97 (t, J = 7.2 Hz, 3H) ppm. ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$): δ 168.8, 164.6, 155.3, 150.8, 145.8, 139.5, 132.7, 132.6, 131.4, 130.2, 129.1, 128.8, 128.3, 127.9, 126.6, 123.9, 123.5, 120.8, 120.3, 116.9, 116.4, 61.5, 56.4, 44.0, 41.8, 30.1, 13.9 ppm. HRMS (SI–TOF) m/z: [M + H]$^+$ calcd for C$_{29}$H$_{25}$N$_2$O$_4$, 465.1809; found: 465.1830.

Ethyl 4-(2-hydroxynaphthalen-1-yl)-3-(5-methylpyridin-2-yl)-2-oxo-6-phenyl-3-azabicyclo [3.1.0] hexane-1-carboxylate (6b)

White solid. Yield: 371 mg (78%). R_f = 0.41 (hexane/EtOAc, 1 : 9 v/v). Mp: 246–248 °C; ^{1}H NMR (400 MHz, CDCl$_3$): δ 8.32 (s, 1H), 8.07 (d, J = 4.8 Hz, 1H), 8.00 (d, J = 8.4 Hz, 1H), 7.93 (d, J = 8.4 Hz, 1H), 7.76–7.68 (m, 2H), 7.41–7.32 (m, 3H), 7.27–7.17 (m, 4H), 6.83 (d, J = 4.4 Hz, 1H), 6.19 (s, 1H), 4.01–3.91 (m, 2H), 3.21 (d, J = 4.4 Hz, 1H), 3.03 (d, J = 4.4 Hz, 2H), 2.25 (s, 3H), 0.87 (t, J = 7.0 Hz, 3H) ppm. ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$): δ 168.8, 164.6, 155.4, 151.3, 150.7, 145.3, 132.8, 131.3, 130.2, 129.1, 128.7, 128.3, 127.9, 126.5, 123.9, 123.4, 121.6, 120.9, 118.5, 117.0, 116.8, 61.5, 56.5, 44.0, 41.8, 30.1, 21.5, 13.9 ppm. HRMS (SI–TOF) m/z: [M + H]$^+$ calcd for C$_{30}$H$_{27}$N$_2$O$_4$, 479.1965; found: 479.1993.

4-(2-Methoxynaphthalen-1-yl)-3,6-diphenyl-3-azabicyclo [3.1.0] hexan-2-one (7)

To a mixture of potassium hydroxide (112 mg, 1.0 mmol) and dimethyl sulphate (63 mg, 0.5 mmol). In THF/MeOH (1 mL, 1 : 1 v/v) was added dropwise a solution of pyrrolidinone 4a (232 mg, 0.5 mmol) in THF/MeOH (1 mL, 1 : 1 v/v) followed by a drop of Et$_3$N. The reaction mixture was heated under reflux for 64 h. After the completion of the reaction, the reaction mixture was cooled to room temperature, a brine solution was added and extracted with ethyl acetate. The organic layer was dried over Na$_2$SO$_4$ and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel using EtOAc/hexane (1 : 4, v/v) to give product 7. Orange solid. Yield: 144 mg (71%). R_f = 0.75 (hexane/EtOAc, 4 : 6 v/v). Mp: 268–270 °C; ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.80–7.76 (m, 4H), 7.47 (t, J = 7.4 Hz, 2H), 7.41 (t, J = 7.4 Hz, 2H), 7.30–7.17 (m, 5H), 6.78 (t, J = 7.4 Hz, 1H), 6.71 (d, J = 7.6 Hz, 2H), 3.95 (d, J = 3.2 Hz, 1H), 3.73–3.66 (m, 2H), 3.49 (s, 3H), 2.80 (t, J = 4.6 Hz, 1H) ppm. ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$): δ 175. 4, 160.4, 154.2, 133.2, 131.9, 129.33, 129.28, 129.1, 128.5, 127.7, 124.4, 123.1, 118.6, 114.4, 110.1, 73.7, 55.4, 41.1, 39.6, 32.2 ppm. HRMS (SI–TOF) m/z: [M + H]$^+$ calcd for C$_{28}$H$_{24}$NO$_2$, 406.1802; found: 406.1808.

4-(2-Hydroxynaphthalen-1-yl)-3-(4-methoxyphenyl)-6-phenyl-3-azabicyclo [3.1.0] hexan-2-one (8)

To a solution of pyrrolidinone **4k** (247 mg, 0.5 mmol) in THF/MeOH (1 mL, 1 : 1 v/v) was added lithium chloride (42 mg, 1.0 mmol). The reaction mixture was heated under reflux for 40 h. After the completion of the reaction, the reaction mixture was cooled to room temperature, a brine solution was added and extracted with ethyl acetate. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel using hexane/EtOAc (2 : 3, v/v) to give product **8**. Yellow oil. Yield: 165 mg (78%). $R_f = 0.68$ (hexane/EtOAc, 2 : 3 v/v). ^1H NMR (400 MHz, $CDCl_3$): δ 8.11 (d, $J = 8.4$ Hz, 1H), 7.84 (d, $J = 8.8$ Hz, 3H), 7.64–7.56 (m, 3H), 7.49–7.42 (m, 3H), 7.30–7.11 (m, 4H), 7.02 (d, $J = 8.0$ Hz, 1H), 5.95 (d, $J = 4.8$ Hz, 1H), 5.42 (d, $J = 11.6$ Hz, 1H), 3.89 (s, 3H), 3.14–3.08 (m, 1H), 2.87 (dd, $J_1 = 8.0$ Hz, $J_2 = 17.6$ Hz, 1H), 2.46 (d, $J = 17.6$ Hz, 1H) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 175.7,157.0, 154.7, 131.7, 130.1, 128.5, 128.0, 127.6, 124.3, 123.2, 121.2, 118.6, 111.0, 110.3, 73.8, 70.8, 55.6, 40.4, 31.8 ppm. HRMS (ESI–TOF) m/z: $[M + H]^+$ calcd for $C_{28}H_{24}NO_3$, 422.1751; found: 422.1757.

Conflicts of interest

There are no conflicts to declare.

Data availability

CCDC 2480506 (**4a**) contain the supplementary crystallographic data for this paper.[9]

The data supporting this article have been included as part of the supplementary information (SI). Supplementary information: copies of ^1H and ^{13}C NMR spectra of all products and X-ray structural information of **4a**. See DOI: https://doi.org/10.1039/d5ra06663h.

Acknowledgements

Notes and references

1 (a) B. B. Toure and D. G. Hall, *Chem. Rev.*, 2009, **109**, 4439–4486; (b) E. Ruijter, R. Scheffelaar and R. V. A. Orru, *Angew. Chem., Int. Ed.*, 2011, **50**, 6234–6246; (c) S. Zhi, X. Ma and W. Zhang, *Org. Biomol. Chem.*, 2019, **17**, 7632–7650; (d)

M. Tandi, V. Sharma, B. Gopal and S. Sundriyal, *RSC Adv.*, 2025, **15**, 1447–1489.

2 (a) M. Arend, B. Westermann and N. Risch, *Angew. Chem., Int. Ed.*, 1998, **37**, 1044–1070; (b) J. M. M. Verkade, L. J. C. van Hemert, P. J. L. M. Quaedflieg and F. P. J. T. Rutjes, *Chem. Soc. Rev.*, 2008, **37**, 29–41; (c) J. F. A. Filho, B. C. Lemos, A. S. de Souza, S. Pinheiro and S. J. Greco, *Tetrahedron*, 2017, **73**, 6977–7004; (d) X. Zhou, Z. Lai, J. Li, C. Fan and S. Cui, *Acc. Chem. Res.*, 2025, **58**, 2317–2331.

3 G. Papeo and M. Pulici, *Molecules*, 2013, **18**, 10870–10900.

4 (a) C. Cardellicchio, M. A. M. Capozzi and F. Naso, *Tetrahedron:Asymmetry*, 2010, **21**, 507–517; (b) A. Olyaei and M. Sadeghpour, *RSC Adv.*, 2019, **9**, 18467–18497; (c) A. Olyaei and M. Sadeghpour, *RSC Adv.*, 2024, **14**, 11811–11848.

5 (a) H. U. Reissig and R. Zimmer, *Chem. Rev.*, 2003, **103**, 1151–1196; (b) M. Yu and B. L Pagenkopf, *Tetrahedron*, 2005, **61**, 321–347; (c) M. Y. Melnikov, E. M. Budynina, O. A. Ivanova and I. V. Trushkov, *Mendeleev Commun.*, 2011, **21**, 293–301; (d) T. F. Schneider, J. Kaschel and D. B. Werz, *Angew. Chem., Int. Ed.*, 2014, **53**, 5504–5523; (e) H. K. Grover, M. R. Emmett and M. A. Kerr, *Org. Biomol. Chem.*, 2015, **13**, 655–671; (f) P. Singh, R. K. Varshnaya, R. Dey and P. Banerjee, *Adv. Synth. Catal.*, 2020, **362**, 1447–1484; (g) Y. Xia, X. Liu and X. Feng, *Angew. Chem., Int. Ed.*, 2021, **60**, 9192–9204; (h) *Donor-Acceptor Cyclopropanes in Organic Synthesis*, ed. P. Banerjee and A. T. Biju, Wiley-VCH, Weinheim, 2024; (i) A. G. Chaidali, M. A. Terzidis and I. N. Lykakis, *Chem. - Eur. J.*, 2025, **31**, e202404791.

6 (a) S. Peraka, A. Hussain and D. B. Ramachary, *J. Org. Chem.*, 2018, **83**, 9795–9817; (b) M. Meenakshi and K. Srinivasan, *Org. Biomol. Chem.*, 2022, **20**, 8741–8746; (c) A. Hussain, S. Peraka and D. B. Ramachary, *J. Org. Chem.*, 2023, **88**, 16047–16064; (d) S. Thangamalar and K. Srinivasan, *J. Org. Chem.*, 2023, **88**, 3903–3908; (e) S. R. Jeny and K. Srinivasan, *J. Org. Chem.*, 2023, **88**, 9395–9400.

7 T. Devaraj and K. Srinivasan, *J. Org. Chem.*, 2024, **89**, 13886–13893.

8 (a) H. Ahankar, A. Ramazeni, K. Slepokura, T. Lis and S. W. Joo, *Green Chem.*, 2016, **18**, 3582–3593; (b) L.-L. Jiang, S.-J. Hu, Q. Xu, H. Zheng and W.-T. Wei, *Chem.–Asian J.*, 2021, **16**, 3068–3081; (c) H. Yin, T. Huang, B. Shi, W. Cao, C. Yu, T. Li, K. Zhang and C. Yao, *Org. Chem. Front.*, 2023, **10**, 2695–2700.

9 CCDC 2480506: Experimental Crystal Structure Determination, 2025, DOI: 10.5517/ccdc.csd.cc2p85bh.

10 A. Shahrisa, R. Teimuri-Mofrad and M. Gholamhosseini-Nazari, *Mol. Diversity*, 2015, **19**, 87–101.