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ORGANIC BASE-CATALYZED CASCADE REACTION OF ELECTRON-DEFICIENT CYCLOPENTADIENONE WITH PROP-2-YN-1-OLS: FORMATION OF 3-METHYLENETETRAHYDROFURAN RING CONDENSED WITH CYCLOPENTENONE

Koki Yamaguchi

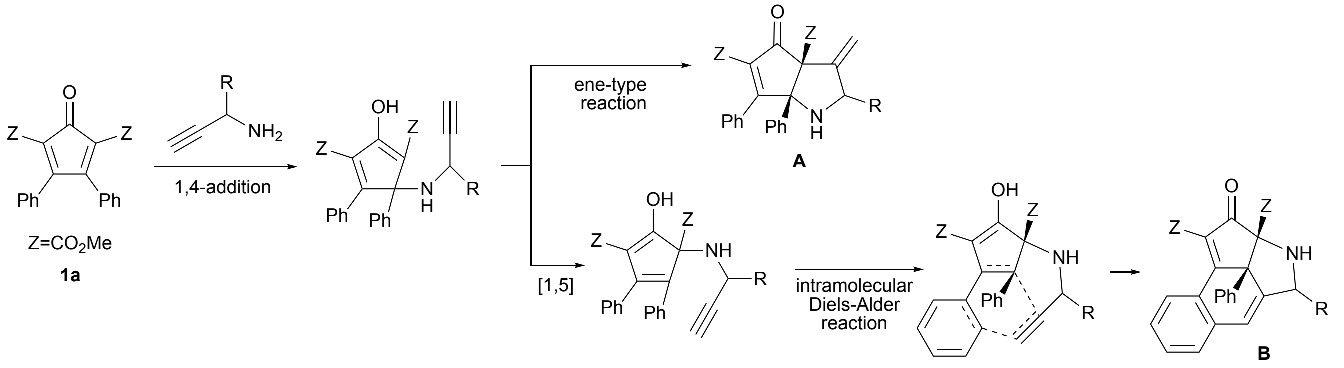
Faculty of Pharmaceutical Sciences, Sojo University, 4-22-1 Ikeda, Nishi-ku, Kumamoto 860-0082, Japan; E-mail address; kyamag05@ph.sojo-u.ac.jp

Abstract – 2,5-Bis(methoxycarbonyl)-3,4-diphenylcyclopentadienone (**1a**) reacts with prop-2-yn-1-ols (**2**) in the presence of 1,4-diazabicyclo[2.2.2]octane at room temperature to produce bicyclic carbocycles (**4**) in moderate yields, as well as tetracyclic carbocycle (**5**). The bicyclic carbocycle, which has a 3-methylenetetrahydrofuran moiety, is derived from the anionic cyclization of the 1,4-adducts of **1a** and **2** onto a non-activated alkyne. The mechanism of the cascade reaction was discussed based on the density functional theory calculations and the X-ray crystallographic analysis.

INTRODUCTION

A cascade reaction is a chemical transformation process involving the generation of a highly reactive intermediate that subsequently undergoes a consecutive series of intramolecular reactions. These reactions have been established as a powerful method of organic synthesis to construct a polycyclic framework. The nature of cascade reactions lends this synthetic method several advantages including efficiency, stereoselectivity and obviation of the necessity to isolate the reaction intermediates generated in the process.[1-4] Therefore, the method satisfies the principles of green chemistry and has become increasingly important from an economic point of view. 2,5-Bis(methoxycarbonyl)-3,4-diphenylcyclopentadienone (**1a**) is powerful 4π synthon owing to the very low energy level of its lowest unoccupied molecular orbital (LUMO). The cycloaddition reaction of **1a** with various dienophiles have been studied extensively,[5-9] with the exception of those involving unsaturated compounds bearing a hydroxy or an amino group. This is due to the preconception that 1,4-addition would occur prior to cycloaddition, given the high propensity of **1a** to form 1,4-adducts with amines or alcohols.[10]

In a previous study of the pericyclic reactions of cyclopentadienones, we found that **1a** reacts with prop-2-yn-1-amines via a cascade reaction pathway to yield bicyclic (A) and tetracyclic (B) compounds.[11] A bicyclic compound was derived from an ene-type reaction of the 1,4-adduct of **1a** and prop-2-yn-1-amine. On the other hand, a tetracyclic compound was formed through [1,5]-sigmatropic rearrangement of the 1,4-adduct, followed by an intramolecular Diels-Alder (DA) reaction (Scheme 1).



Scheme 1. Cascade reaction of **1a** and prop-2-yn-1-amines

Along the same lines, we reported the novel cyclization reactions of **1a** with prop-2-yn-1-ols (**2**)[12] and but-3-yn-2-ones[13] in the presence of trialkylamines. Preliminarily PM3[14] calculations show that the highest occupied molecular orbital (HOMO) of prop-2-yn-1-ol (**2a**) is localized on the double bond (π-HOMO), whereas the HOMO of its conjugated base (alkoxide) is localized on the oxygen atom (n-HOMO). It was predicted that inversion of the π and n orbital energy levels of **2a**, through conversion to the alkoxide, would lead to preference for the 1,4-addition reaction over the Diels-Alder reaction (Figure 1).

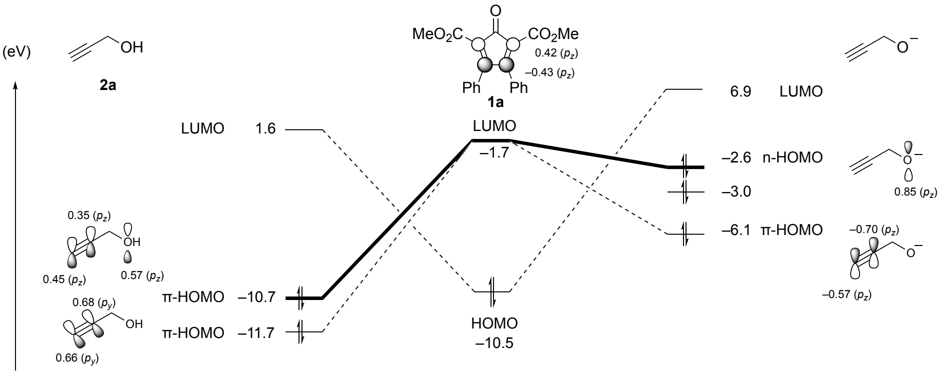


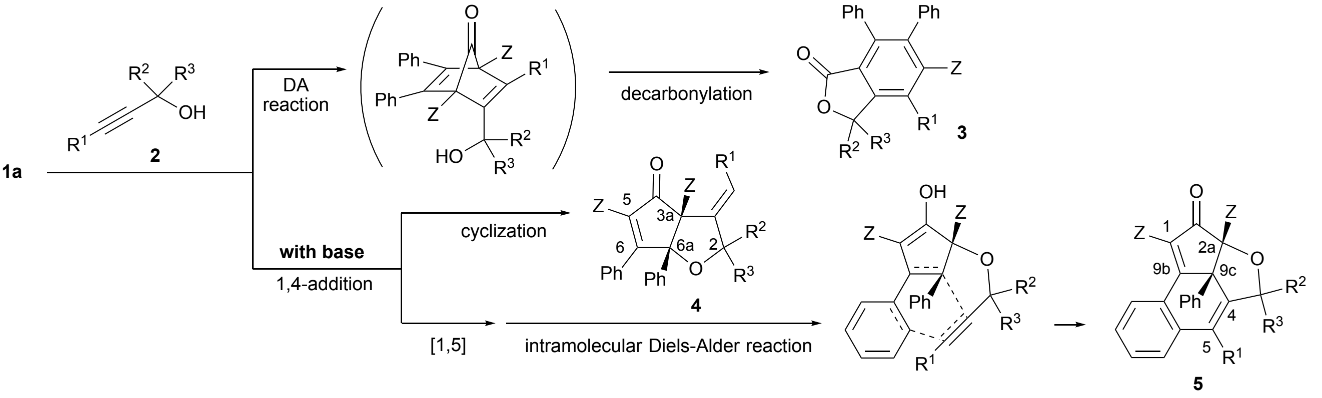
Figure 1. PM3-calculated FMO energies and coefficients

This paper describes a detailed discussion of new experimental and theoretical data for the reaction between **1a** and **2** to elucidate the overall mechanism of the reaction.

RESULTS AND DISCUSSION

Reaction of 1a with prop-2-yn-1-ols (2a-k) in the presence of trialkylamines

The reaction of **1a** with prop-2-yn-1-ols (**2**) was known to give the substituted phthalide derivative **3** via decarbonylation of the DA adduct. In contrast, in the presence of a catalytic amount of 1,4-diazabicyclo[2.2.2]octane (DABCO), the reaction of **1a** with **2a** in $CHCl_3$ at room temperature gave bicyclic compound (**4a)** in good yield (84%) (Scheme 2). Similar yields were obtained in toluene. When toluene was used as a solvent, the tetracyclic compound **5** was not produced regardless of the type of catalyst. The structure of **4a** was determined by ^1H and ^{13}C NMR spectra and confirmed unambigously by single crystal X-ray analysis (see Supporting Information Figure S1). The formation of **4a** indicates that the alkoxide anion generated by DABCO is more reactive than the acetylenic π orbital, in accordance with the frontier molecular orbital (FMO) analysis. A good yield of the bicyclic compound **4a** was also obtained using triethylamine (TEA) as the catalyst.



Scheme 2. Cascade reaction of **1a** and prop-2-yn-1-ols (**2**)

The reaction conditions are summarized in Table 1. In the reaction of but-3-yn-2-ol (**2b**) with **1a**, a mixture of *exo*-**4b** and *endo*-**4b** (*ca.* 1:1) was obtained. X-Ray structure analysis of the product revealed that *exo*-**4b** and *endo*-**4b** form a 1:1 co-crystal (Figure 2). The C2-Me protons of *endo*-**4b** shifted further upfield (δ 1.41) relative to that of *exo*-**4b** (δ 1.58) due to the anisotropic effect of the C5–C6 double bond.

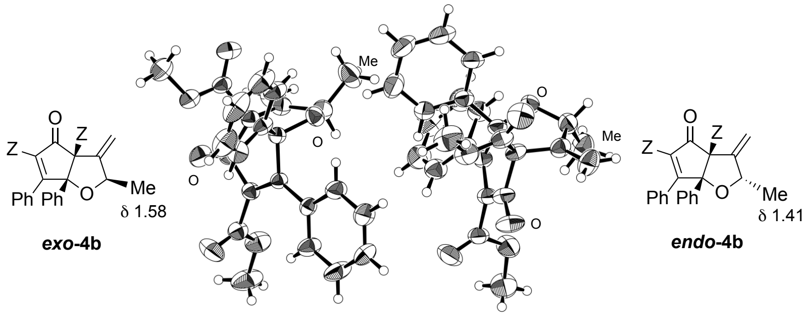
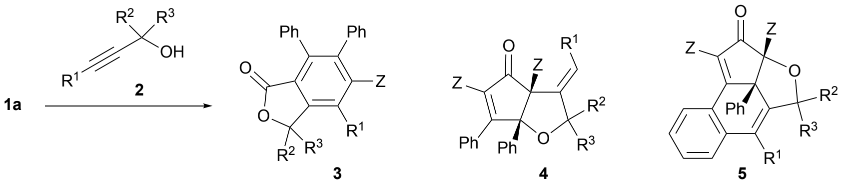


Figure 2. X-Ray structures of *exo*-**4b** and *endo*-**4b** involved in the asymmetric unit of the co-crystal and the ^1H NMR chemical shifts of methyl groups

Table 1. Product distribution for the reaction of **1a** with **2a-2k** at room temperature[a]



Compd.	substituents			solvent	base	time (d)	products		
	R1	R2	R3				**3**	**4**	**5**
2a	H	H	H	$CHCl_3$	DABCO[b]	2	0	84	0
				$CHCl_3$	TEA[b]	1	0	70	0
				toluene	DABCO[c]	2	0	92	0
				toluene	TEA[c]	1	0	95	0
				DMF	DABCO[b]	1	0	65	0
				TEA	TEA	3	0	67	0
				$CHCl_3$[d]	–	1	83	0	0
2b	H	Me	H	$CHCl_3$	DABCO[d]	3	14	54[h]	0
2c	H	Me	Me	THF	LDA[f]	7	0	4	14
2d	H	$-(CH_2)_4-$		THF	LDA[f]	2	0	5	10
				toluene	P_4-*t*-Bu[g]	3	0	80	0
2e	H	$-(CH_2)_5-$		THF	LDA[f]	2	0	8	12
2f	Ph	H	H	toluene	DABCO[c]	4	40	46	0
2g	1-naphthyl	H	H	toluene	DABCO[c]	1	0	46	0
2h	Me	H	H	$CHCl_3$	DABCO[e]	6	34	0	16
2i	Et	H	H	$CHCl_3$	DABCO[e]	5	39	0	13
2j	CH_2OH	H	H	$CHCl_3$	DABCO[b]	1	0	82	0
2k	$C(Me)_2OH$	Me	Me	THF	LDA[f]	6	0	6	0
				toluene	P_4-*t*-Bu[g]	3	0	57	0

[a] A portion of this data has already reported as a communication (ref. 12).

[b] **2**:base=1:1/24. [c] **2**:base=1:1/30. [d] 60 °C. [e] **2**:base=1:1/5. [f] **2**:base=1:1/2. [g] **2**:base=1:1/4. [h] *endo*:*exo*=22:32.

Substitution at the 1-position of **2** has a significant effect on the formation of the bicyclic compound **4**. Introduction of a methyl group at the 1-position (**2b**) retarded the formation of **4b** while introduction of additional alkyl groups (tertiary alcohols **2c-e**) did not lead to the formation of any cyclization product in the presence of either DABCO or TEA.

The reaction with 3-phenyl derivative (**2f**) produced a bicyclic compound (**4f**), as well as decarbonylated DA adduct (**3f**). The chemical shift of the C3a-CO_2Me protons in **4f** is δ 2.67, which comes at the higher field. The upfield shift was attributed to the anisotropic effect of the two neighboring phenyl rings. X-Ray structure analysis confirmed that **4f** has the *E*-form (Figure 3).

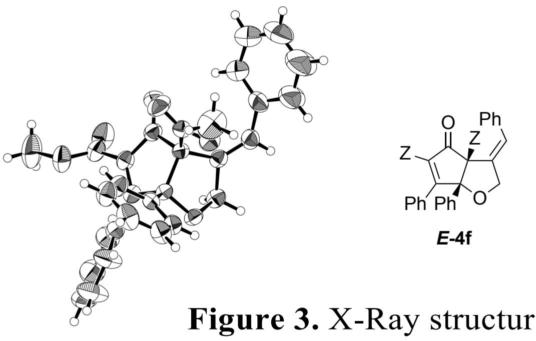


Figure 3. X-Ray structure of ***E*-4f**

In the reaction with naphthyl derivative **2g**, corresponding bicyclic compound **4g** was obtained in 46% yield. The ^{1}H NMR spectrum showed a duplicated signal pattern suggesting that the product is a mixture of *E*- and *Z*-isomer. Inspection of the CO_2Me protons signals indicates that the *E*:*Z* product ratio is 85:15. The major product was assigned to be *E*-isomer because further upfield shift of C3a-CO_2Me protons (δ 2.13) was observed.

In contrast to **2f**, the reaction of 3-alkyl-prop-2-yn-1-ols (**2h** and **2i**) with **1a** did not yield the bicyclic compound. The tetracyclic compound **5h** and the phthalide derivative **3h** were instead obtained from the reaction of 3-methylprop-2-yn-1-ol (**2h**) with **1a** in the presence of DABCO. The mass spectrum of **5h** indicated a dehydrogenated 1:1 adduct of **1a** and **2h**. The characteristic signals of the exocyclic vinyl protons of the bicyclic compound were also absent in the ^{1}H NMR spectrum.

The heteronuclear multiple-bond correlation (HMBC) spectra indicated the presence of nine aromatic protons, which suggests that the terminal carbon of the propargyl group is connected to the 2-position of the phenyl group. The reaction of **1a** with 3-ethylprop-2-yn-1-ol (**2i**) produced the corresponding tetracyclic compound **5i**, whose structure was confirmed by X-ray analysis (Figure S1).

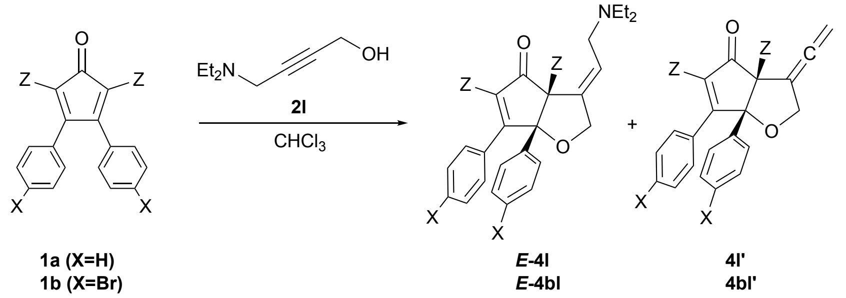
The formation of **5h** is assumed to proceed similarly through the previously proposed reaction mechanism with propargylamines.[11] That is, **5h** was formed via [1,5]-sigmatropic rearrangement of the 1,4-adduct of **1a** and **2h**, followed by an intramolecular Diels-Alder reaction (with the styrene moiety as diene) and dehydrogenation of the resulting adduct.

Compound **2j** immediately underwent cyclization to yield the bicyclic compound ***E*-4j** exclusively, implying that hydrogen bonding between the hydroxymethyl group and carbonyl oxygen might promote the cyclization.

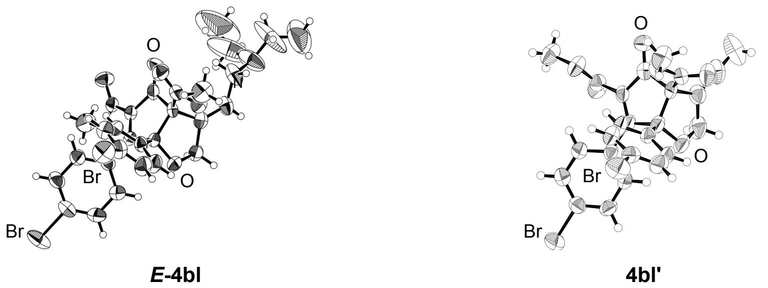
As stated above, trialkylamines were not able to catalyze the formation of the bicyclic compound from tertiary alcohols, which prompted the use of stronger bases. Lithium diisopropylamide (LDA) catalyzed the reaction of **1a** and **2d** to form **4d**, albeit with a low yield. On the other hand, phosphazene base P4-*t*-Bu,[15,16] which is known to be very potent and hindered neutral nitrogen base, greatly increased the yield of **4d** as solo product, in contrust to that for LDA catalysis. These results suggest that the transition state for bicyclic compound formation is more effectively stabilized by phosphazene base than by LDA. The reaction of **1a** with **2k** under similar conditions yielded the *E*-isomer of **4k**, as confirmed by X-ray structure analysis (Figure S1). The hydroxy group forms an intramolecular hydrogen-bond with the carbonyl oxygen of the cyclopentenone moiety [the O•••O and O–H•••O distances are 2.741(3) and 1.829(2) Å, respectively].

Reaction of 1a with 4-(diethylamino)but-2-yn-1-ol (2l)

4-(Diethylamino)but-2-yn-1-ol (**2l**), in which the trialkylamine moiety is incorporated in the compound, was also used as a reactant (Scheme 3).



Scheme 3. Cascade reaction of **1** and **2l**



E-4bl

4bl'

Figure 4. X-Ray structures of ***E*-4bl** and **4bl'**

Stirring of the reaction mixture of **1a** and **2l** in $CHCl_3$ for one day at room temperature yielded the bicyclic compounds ***E*-4l** (73%) and **4l'** (14%). The ^{1}H NMR spectrum of **4l'** also exhibited the characteristic split signals of the methyl protons of methoxycarbonyl (δ 3.85 and 3.09) and the exocyclic vinyl protons. However, the ethyl proton signals of the diethylamino group were absent. Compound **4l'** exhibited an $[M+Na]^+$ ion peak at *m/z* 439 in the mass spectrum, suggesting that the elimination of Et_2NH from **4l** occurred to form the bicyclic compound including an allene moiety. The structures of **4l** and **4l'** were deduced through comparison of its ^{1}H NMR spectra with those of ***E*-4bl** and **4bl'**. The products were derived from the reaction of 2,5-bis(methoxycarbonyl)-3,4-di(4-bromophenyl)cyclopentadienone (**1b**) and **2l**, and those structures have been confirmed by X-ray analysis (Figure 4). The formation of **4l** indicates that **2l** acts as a self-catalyst.

Reaction mechanism

It was previously assumed that the bicyclic compound **4** is derived from an intramolecular ene-type reaction.[12] However, a concerted cyclic mechanism cannot explain the preference formation of the *E*-isomer of **4** [i.e., ***E*-4f,g,j,k**], which suggests that the reaction proceeds through a stepwise mechanism.

Careful monitoring of the progress of the reaction between **1a** and **2a** in different polarity of solvents by ^{1}H NMR spectroscopy revealed the ionic reaction nature. A plot of the concentration of **4a** against time is depicted in Figure 5.

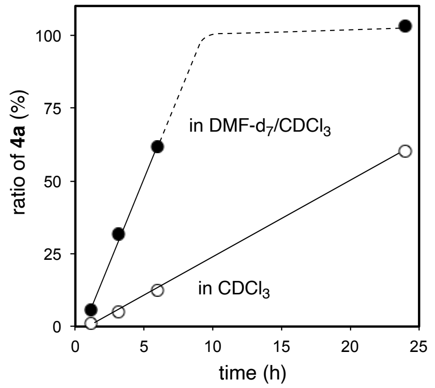
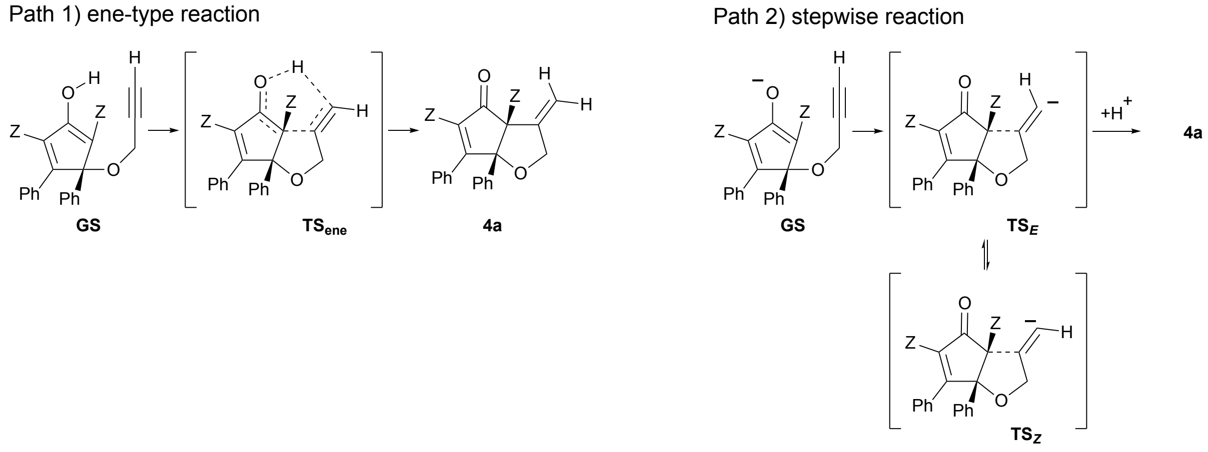


Figure 5. Time course for the reaction of **1a** with **2a**

The rate for the formation of **4a** at the initial reaction stage in DMF-d_7/$CDCl_3$[17] (molar transition energy polarity value, E_T=43.3[18]) was 0.92, which was ca. 4.4 times larger than that in $CDCl_3$ (E_T=39.1[18]). Moderate acceleration of the reaction rate in the dipolar aprotic solvent suggested that the transition state appears to have more carbanionic-like character.

Dumez et al.[19] reported an intriguing reaction involving the formation of 3-methylenetetrahydrofurans through a Michael addition-carbocyclization cascade reaction of nitroalkenes and propyn-1-ols in the presence of *t*-BuOK. The authors hypothesized that the reaction proceeds via anionic intramolecular cyclization onto an alkyne. In a similar manner, the formation of **4** may proceed through a stepwise mechanism via an anionic transition state. Thus, two possible reaction pathways for the formation of **4** were investigated (Scheme 4): (a) the ene-type reaction that was previously considered[12] (path 1) and (b) the stepwise reaction via a carbanionic transition state (both *E* and *Z* isomers), which subsequently undergoes irreversible protonation (path 2).

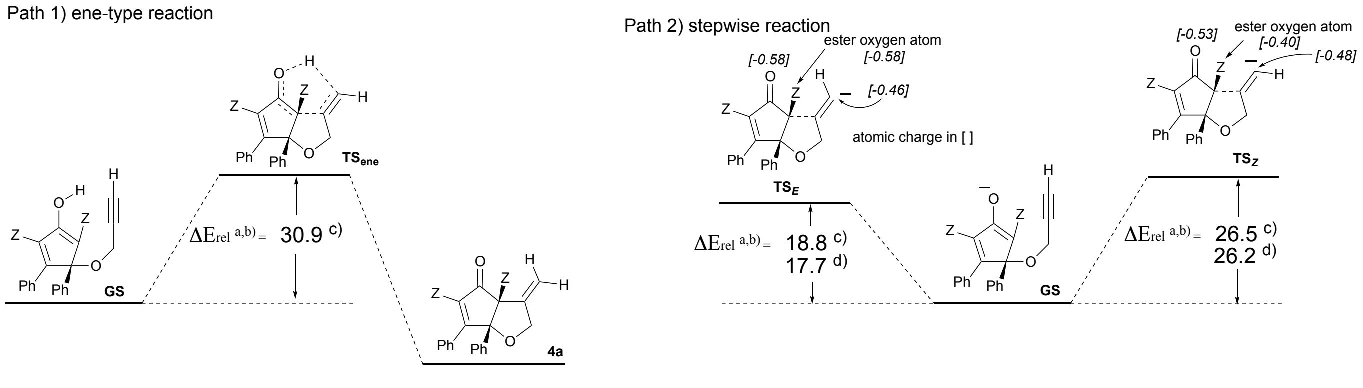


Scheme 4. Possible reaction pathways

The energy profiles of each reaction pathway, obtained from DFT calculations[20] at the B3LYP/6-31G(d) and B3LYP/6-31G+(d) levels, were examined to elucidate the reaction mechanism. The energy profiles and the transition state (TS) structures for the reaction of **1a** and **2** are depicted in Figure 6.

The energy barriers for the ene-type and stepwise reactions were estimated to be 30.9 and 18.8 (via TS_E) kcal/mol, respectively, at the B3LYP/6-31G(d) level. The estimated activation barrier for the ene-type reaction concurs well with the available calculated data [31.2 kcal/mol at MP2/6-31G(d)//3-21G level] and the experimental data (ca. 35 kcal/mol) for the reaction of propene and ethylene.[21] The energy barrier for the stepwise reaction at the B3LYP/6-31G+(d) level, on the other hand, is 17.7 kcal/mol. The calculated values suggest that formation of **4a** via a cabanionic transition state is energetically more favorable than the ene-type reaction pathway.

The stereochemistry of **4a** appears to be associated with the configurational stability of the vinylic anion at the transition state. TS_E, which leads to the *E*-isomer of the adduct, is considerably more stable than TS_Z by 8.5 kcal/mol at the B3LYP/6-31+G(d) level(Figure 6). The vinylic anion equilibrium between the two isomers disfavors TS_Z due to the repulsion between the lone-pair orbital of the vinyl anion and the enone-carbonyl oxygen atom, as well as the ester oxygen atom. The distance between the carbon and oxygen atoms is 3.554 Å in the former and 3.341 Å in the latter (see Supporting Information Figure S2).

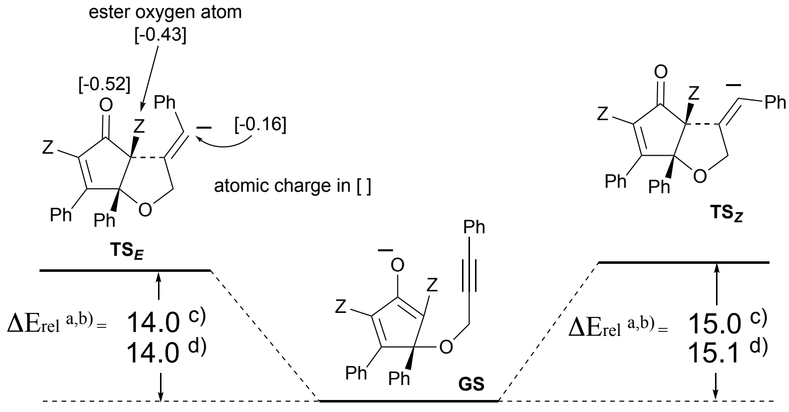


[a] Potential energy barriers relative to E_{ZPE} of GS. [b] kcal/mol. [c] B3LYP/6-31G(d). [d] B3LYP/6-31G+(d).

Figure 6. Calculated atomic charge and reaction barriers of the two possible reaction pathways of **1a** and **2a**

The reaction barrier for the formation of ***E*-4f** was estimated to be 14.0 kcal/mol at the B3LYP/6-31+G(d) level. The lower barrier, relative to that of **4a**, can be attributed to the stabilization of the vinyl anion by the phenyl group through resonance interaction. TS_E, in this case, is more stable than TS_Z only 1.1 kcal/mol, which is in accordance with the observed small formation of ***Z*-4g**. In addition, the delocalization of the atomic charge on the carbanion of TS_E

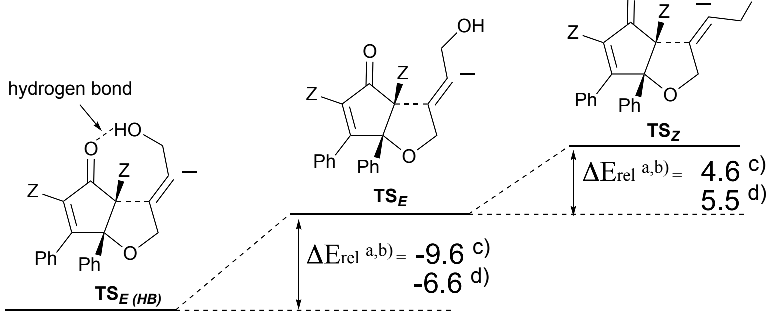
(–0.16) may be favorable to cyclization, in comparison with the case of TS*E* leading to **4a** (Figure 7). The strong stabilization of the carbanionic center resulting from charge delocalization suggests that the introduction of an alkyl group at 3-position of **2** would disfavor an anionic transition state formation(Figure S3). This was confirmed by the fact that the formation of a bicyclic compound was not observed for the reactions of **1a** with **2h** and **2i**.



[a] Potential energy barriers relative to E_{ZPE} of GS. [b] kcal/mol. [c] B3LYP/6-31G(d). [d] B3LYP/6-31G+(d).

Figure 7. Calculated atomic charge and reaction barriers leading to *E*, *Z*-isomers for the stepwise reaction pathway of **1a** and **2f**

On the other hand, the *E*-form of the bicyclic compound was exclusively produced in the reaction with **2j**, which has a 3-hydroxymethyl substituent. The corresponding TS*E* was 4.6 kcal/mol more stable than TS*Z* at the B3LYP/6-31G(d) level (Figure 8). This energy difference increased to 5.5 kcal/mol with the addition of diffuse functions to the basis set [6-31G+(d)]. The strong intramolecular hydrogen bond between the hydroxy group and carbonyl oxygen in the TS*E* structure (O•••H-O, 1.916 Å in TS*E*(HB)) further enhances the relative stability of the *E* configuration and promotes the cyclization reaction (Figure S4).



[a] Potential energy barriers relative to E_{ZPE} of TS*E*. [b] kcal/mol. [c] B3LYP/6-31G(d). [d] B3LYP/6-31G+(d).

Figure 8. Calculated TS energies for the stepwise reaction pathway of **1a** and **2j**

CONCLUSIONS

In conclusion, we have developed an efficient method for the synthesis of bicyclic carbocycles from the electron-deficient cyclopentadienone (**1a**) and prop-2-yn-1-ols (**2**) using DABCO as the catalyst. The reaction proceeds through the initial formation of a 1,4-adduct, followed by anionic intramolecular cyclization onto a nonactivated alkyne to yield a 3-methylenetetrahydrofuran moiety.

EXPERIMENTAL

The melting points were uncorrected. The IR spectra were recorded using a Hitachi 270-30 spectrophotometer. The ^{1}H NMR and ^{13}C NMR spectra were recorded using JEOL JNM-EX JNM-A 500 (500 MHz) spectrometers in ca.10% solution with tetramethylsilane as the internal standard. The mass spectra were obtained using JMS-DX303HF. Computation: The TS geometries were optimized by DFT method using B3LYP functional at the 6-31G(d) and 6-31+G(d) level. The energies were corrected using zero-point vibrational energy [scaled by a factor of 0.9804[22] for 6-31G(d) and 0.980[23] for 6-31+G(d)]. All the electronic structure calculations were performed by the Gaussian09 package.[20] The DFT calculation data (Cartesian coordinates) are available upon request.

Reaction of 1a and 2a-k with DABCO (general procedure)

A solution of **1a** (0.50 g, 1.4 mmol), 2-propyn-1-ol (**2a**) (0.24 g, 4.3 mmol) and DABCO (20 mg, 0.18 mmol) in $CHCl_3$ (3 mL) was stirred at room temperature for 1 day. After evaporation of the solvent, the residue was chromatographed on silica gel using benzene–AcOEt eluent to give the bicyclic compound **4a** (488 mg, 84%).

Compound 4a: colorless prisms; mp 84–85 °C (from EtOH); IR (KBr) cm^{-1}: 1742, 1710 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.11 (3H, s, C3a-CO_2CH_3), 3.86 (3H, s, C5-CO_2CH_3), 4.55 (1H, ddd, *J* = 13.2, 2.3, 2.3 Hz, 2-H_{endo}), 4.91 (1H, ddd, *J* = 13.2, 2.3, 2.3 Hz, 2-H_{exo}), 5.32 (1H, brs, =CH_2), 5.45 (1H, brs, =CH_2), 7.26–7.38 (8H, m, Ph), 7.42 (2H, d, *J* = 8.6 Hz, Ph); ^{13}C NMR (125 MHz, $CDCl_3$) δ 52.1 (C3a-CO_2CH_3), 52.7 (C5-CO_2CH_3), 71.5 (C2), 73.7 (C3a), 98.1 (C6a), 111.6 (=CH_2), 126.4, 128.2, 128.6, 128.7, 129.5, 131.3 (aromatic CH), 130.8, 134.4, 136.6 (*sp^2* quaternary C), 143.3 (C3), 164.1 (C5-COO), 167.5 (C3a-COO), 168.3 (C6), 192.2 (C=O); MS (FAB, *m/z*): 405 (M^++1). Anal. Calcd for $C_{24}H_{20}O_6$: C, 71.28; H, 4.98. Found: C, 71.13; H, 5.05.

With LDA

A solution of **1a** (0.50 g, 1.4 mmol), 3-methyl-1-butyn-3-ol (**2c**) (0.20 g, 2.4 mmol) and LDA (1.4 mmol) in THF (3 mL) was stirred at room temperature for 4 days. After evaporation of the solvent, the residue was chromatographed on silica gel using toluene–AcOEt eluents to give the bicyclic compound **4c** (85 mg, 14%) and the tetracyclic compound **5c** (90 mg, 15%).

Compound 4c: colorless prisms; mp 163–165 °C; IR (KBr) cm^{-1}: 1748, 1738, 1708 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.36 (3H, s, C2-CH_3 (*endo*)), 1.69 (3H, s, C2-CH_3 (*exo*)), 3.08 (3H, s, C3a-$COOCH_3$), 3.85 (3H, s, C5-CO_2CH_3), 5.18 (1H, s, =CH_2), 5.44 (1H, s, =CH_2), 7.24–7.34 (8H, m, Ph), 7.48 (2H, d, J = 7.5 Hz, Ph) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 29.7, 30.7 (C2-CH_3), 52.0 (C3a-CO_2CH_3), 52.7 (C5-CO_2CH_3), 75.0 (C3a), 87.4 (C2), 95.5 (C6a), 111.0 (=CH_2), 126.5, 128.0, 128.4, 128.5, 129.8, 131.2 (aromatic CH), 131.3, 132.8, 137.6 (sp^2 quaternary C), 152.1 (C3), 164.4 (C5-COO), 167.8 (C3a-COO), 170.2 (C6), 193.0 (C=O) ppm; MS (FAB, *m/z*): 433 (M^++H). Anal. Calcd for $C_{26}H_{24}O_6$: C, 72.21; H, 5.59. Found: C, 72.13; H, 5.63.

Compound 5c: yellow prisms; mp 175–177 °C; IR (KBr) cm^{-1}: 1731 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.63 (3H, s, C4-CH_3), 1.80 (3H, s, C4-CH_3), 3.28 (3H, s, C2a-CO_2CH_3), 3.86 (3H, s, C1-CO_2CH_3), 6.36 (1H, s, C5-H), 7.06 (1H, d, J = 7.5 Hz, aromatic H), 7.15–7.19 (4H, m, aromatic H), 7.25–7.29 (3H, m, aromatic H), 7.74 (1H, d, J = 7.5 Hz, aromatic H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ = 27.3, 29.5 (C4-CH_3), 51.9 (C2a-CO_2CH_3), 52.4 (C1-CO_2CH_3), 67.1 (C9c), 88.9 (C4), 89.4 (C2a), 120.3 (C5), 127.4, 127.8, 127.9, 128.2, 128.4, 129.1, 132.0 (aromatic CH), 127.2, 128.7, 133.5, 135.5, 153.2 (sp^2 quaternary C), 162.3 (C1-COO), 168.9 (C2a-COO), 181.1 (C9b), 196.5 (C=O) ppm. HRMS (ESI$^+$, *m/z*) Calcd for $C_{26}H_{22}O_6Na$ (M^++Na): 453.13141. Found: 453.13040.

With P4-*t*-Bu

A solution of **1a** (0.50 g, 1.4 mmol), 1-ethynylcyclopentanol (**2d**) (0.16 g, 1.4 mmol) and P4-*t*-Bu (0.35 mL of 1M hexane solution, 0.35 mmol) in dry toluene (3 mL) was stirred at room temperature for 3 day. After evaporation of the solvent, the residue was chromatographed on silica gel to give the bicyclic compound **4d** (514 mg, 80%).

Compound 4d: Colorless prisms; mp 211–213 °C; IR (KBr) cm^{-1}: 1742, 1712 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.62–1.89 (6H, m, -CH_2-), 2.01–2.08 (1H, m, -CH_2-), 2.38–2.41 (1H, m, -CH_2-), 3.07 (3H, s, C3a-CO_2CH_3), 3.87 (3H, s, C5-CO_2CH_3), 5.22 (1H, s, =CH_2), 5.41 (1H, s, =CH_2), 7.23–7.36 (8H, m, Ph), 7.52 (2H, br d, J = 7.7 Hz, Ph) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 24.0, 25.1, 41.8, 42.8 (-CH_2-), 52.0 (C3a-CO_2CH_3), 52.7 (C5-CO_2CH_3), 75.1 (C3a), 95.3 (C6a), 96.6 (C2), 110.5 (=CH_2), 126.6, 128.0, 128.4, 128.5, 129.8, 131.2 (aromatic CH), 131.4, 133.2, 137.6 (sp^2 quaternary C), 151.2 (C3), 164.6 (C6), 167.8 (C5-COO), 169.6 (C3a-COO), 193.3 (C=O) ppm; MS (FAB, *m/z*): 459 (M^++H). Anal. Calcd for $C_{28}H_{26}O_6$: C, 73.35; H, 5.72. Found: C, 73.33; H, 5.76.

Reaction of 1a and 2l

A solution of **1a** (0.50 g, 1.4 mmol), 4-(diethylamino)but-2-yn-1-ol (**2l**) (0.20 g, 1.6 mmol) in $CHCl_3$ (3 mL) was stirred at room temperature for 1 day. After evaporation of the solvent, the residue was chromatographed on silica gel using *n*-hexane–AcOEt eluent to give the bicyclic compounds **4l** (498 mg, 73%) and **4l'** (82 mg, 14%).

Compound 4l: Brown oil; IR (KBr) cm^{-1}: 1741, 1713 (C=O); ^1H NMR (500 MHz, $CDCl_3$) δ 1.01 (6H, t, *J* = 7.2 Hz, $-CH_2CH_3$), 2.40 (2H, dq, *J* = 20.1, 7.2 Hz, $-CH_2CH_3$), 2.56 (2H, dq, *J* = 20.1, 7.2 Hz, $-CH_2CH_3$), 3.08 (1H, br d, *J* = 16.0 Hz, $-CH=CH_2-N-$), 3.09 (3H, s, C3a-CO_2CH_3), 3.31 (1H, br d, *J* = 16.0 Hz, $-CH=CH_2-N-$), 3.84 (3H, s, C5-CO_2CH_3), 4.44 (1H, dd, *J* = 12.6, 2.9 Hz, C2-H), 4.79 (1H, d, *J* = 12.6 Hz, C2-H), 5.83 (1H, br s, =CH-), 7.24–7.38 (10H, m, Ph) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 11.9 ($-CH_2CH_3$), 47.1 ($-CH_2CH_3$), 52.0 (C3a-CO_2CH_3), 52.2 ($-CH=CH_2-N-$), 52.7 (C5-CO_2CH_3), 71.4 (C2), 72.5 (C3a), 98.8 (C6a), 127.9, 128.1, 128.5, 128.7, 129.3, 131.3 (aromatic CH), 130.6, 134.8, 135.3, 136.2 (*sp^2* quaternary C), 164.1 (C5-COO), 167.3 (C3a-COO), 167.5 (C6), 191.1 (C=O) ppm. HRMS (ESI^+, *m/z)* Calcd for $C_{29}H_{32}NO_6$ (M^++H): 490.22296. Found: 490.22333.

Compound 4l': pale yelleow powder; mp 74–76 °C; IR (KBr) cm^{-1}: 1742 (C=O); ^1H NMR (500 MHz, $CDCl_3$) δ 3.09 (3H, s, C3a-CO_2CH_3), 3.85 (3H, s, C5-CO_2CH_3), 4.55 (1H, dt, *J* = 12.0, 4.6 Hz, C2-H), 4.92 (1H, dt, *J* = 12.0, 3.4 Hz, C2-H), 5.14 (1H, ddd, *J* = 12.0, 4.6, 3.4 Hz, $=CH_2$), 5.22 (1H, ddd, *J* = 12.0, 4.6, 3.4 Hz, $=CH_2$), 7.24–7.36 (8H, m, Ph), 7.44 (2H, d, *J* = 8.0 Hz, Ph) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 52.0 (C3a-CO_2CH_3), 52.6 (C5-CO_2CH_3), 68.6 (C2), 72.5 (C3a), 82.7 ($=CH_2$), 97.8 (C6a), 100.1 (C3), 126.4, 127.2, 128.0, 128.3, 128.4, 128.5, 128.7, 128.8, 129.4, 131.3 (aromatic CH), 130.5, 134.7, 136.1 (*sp^2* quaternary C), 164.0 (C5-COO), 166.9 (C3a-COO), 167.3 (C6), 191.8 (C=O), 201.5 ($C=C=CH_2$) ppm. HRMS (ESI^+, *m/z*) Calcd for $C_{25}H_{20}O_6Na$ (M^++Na): 439.11576. Found: 439.11324.

Time course

A $CDCl_3$ solution (1.8 mL) containing **1a** (167 mg, 0.48 mmol), **2a** (80 mg, 1.4 mmol) and DABCO (6.7 mg, 0.060 mmol) was placed in a sealed test tube, which was stirred at room temperature. An aliquot (50 μL) of the reaction mixture was taken at appropriate sampling interval, and was diluted with $CDCl_3$. The reaction was monitored by analysis of the ^1H NMR signals of the OMe group of **4a** and the methylene group of DABCO. Similar analysis was applied to the reaction in $CDCl_3$/DMF-d_7 (1.1 / 0.7 mL) binary solvent mixture.

X-Ray crystallography

The single crystals were prepared by slow evaporation of solution at room temperature. All measurements were performed on a Rigaku RAXIS RAPID imaging plate area detector with graphite-monochromated

Mo-Kα radiation (λ= 0.71075 Å). The data were collected at a temperature of 23±1°C to a maximum 2θ value of 54.8°. The structure was solved by direct method (SIR92[24]), and all hydrogen atoms were located at calculated positions. The structure was refined by a full-matrix least-squares technique using anisotropic thermal parameters for non-hydrogen atoms and a riding model for hydrogen atoms. All calculations were performed using the crystallographic software package Crystal Structure.[25] These X-ray crystallographic data have been deposited at the Cambridge Crystallographic Data Centre (CCDC).

Crystal Data of 4b: $C_{50}H_{44}O_{12}$, M=836.89, monoclinic, space group *P2₁*, a=9.9039 (7), b=23.377 (2), c=9.9678 (6) Å, β=112.128 (2)°, V=2137.8 (3) $Å^3$, Dc=1.300 gcm^{-3}, Z=2, R=0.050, Rw=0.081. CCDC reference number 1010116. ***E*-4f:** $C_{30}H_{24}O_6$, M=480.52, monoclinic, space group $P2_1/n$, a=12.204 (2), b=11.2716 (9), c=18.418 (2) Å, β=90.987 (3)°, V=2533.2 (4) $Å^3$, Dc=1.260 gcm^{-3}, Z=4, R=0.067, Rw=0.108. CCDC reference number 1010115. **4bl:** $C_{29}H_{29}NO_6Br_2$, M=647.36, triclinic, space group P–1, a=10.391 (1), b=11.932 (2), c=12.339 (2) Å, α=69.645 (3), β=85.600 (3), γ=81.636 (3)°, V=1421.2 (3) $Å^3$, Dc=1.513 gcm^{-3}, Z=2, R=0.051, Rw=0.074. CCDC reference number 1010114. **4bl':** $C_{25}H_{18}O_6Br_2$, M=574.22, monoclinic, space group $P2_1/c$, a=13.9258 (8), b=9.5909 (5), c=17.500 (1) Å, β=92.588 (3)°, V=2335.0 (2) $Å^3$, Dc=1.633 gcm^{-3}, Z=4, R=0.086, Rw=0.145. CCDC reference number 1010117.

SUPPORTING INFORMATION

^1H NMR, ^{13}C NMR, IR and Mass spectra of all compounds in Table 1 are available.

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