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Graphical Abstract

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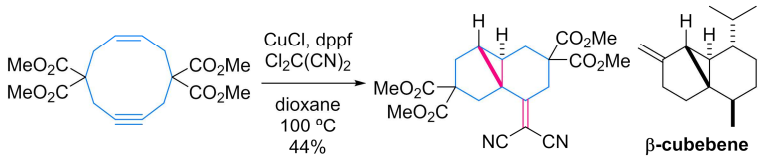

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ABSTRACT

A Cu-catalyzed radical reaction of $Cl_2C(CN)_2$ was utilized for stereoselective conversion of unsaturated molecules into functionalized carbocycles. Chloromalononitrile radicals, generated by treating $Cl_2C(CN)_2$ with catalytic amounts of CuCl and dppf in refluxing dioxane, intermolecularly reacted with the unsaturated bonds of acyclic or 10-membered compounds. The resultant carboradicals then intramolecularly added to another unsaturated bond to produce 1,2-disubstituted cyclopentane or *trans*-decalin derivatives. The chemo- and stereoselectivities of these radical cascade reactions are discussed in detail.

1. Introduction

Carbocycles are ubiquitously present in functional materials, pharmaceuticals, and natural products. Historically, extensive synthetic efforts have been devoted to the development of efficient strategies and tactics for carbocycle construction. A highly attractive approach to streamline the synthesis of carbocycles is cascade reactions, which enable multiple carbon-carbon (C-C) bond formations in a single step.[1] In particular, radical-based cascade reactions are neutral, yet powerful, and allow for effective assembly of the functionalized carbocyclic motifs that are difficult to construct with conventional cationic/anionic or pericyclic reactions.[2]

We previously reported a Cu-catalyzed atom transfer radical addition of $Cl_2C(CN)_2$ to electronically non-polarized double bonds to form the two new bonds highlighted in red (Scheme 1A).[3,4,5] Outcomes of the reactions depended on the substrate structures: carbochlorination proceeded from mono-substituted alkenes (R^1=R^2=H), whereas carbocyanation underwent from trisubstituted alkenes (R^1=R^2=Me). Namely, the addition of chloromalononitrile radicals generated from $Cl_2C(CN)_2$ occurred at the less-hindered position of the double bonds of the substrates. Then, intermolecular chlorination of the resultant secondary carboradicals provided the 1,3-dichlorinated product. On the other hand, chlorination of the tertiary radical was slower, and intramolecular cyanide transfer occurred prior to the intermolecular chlorination, giving rise to the 1,3-dicyanated product.

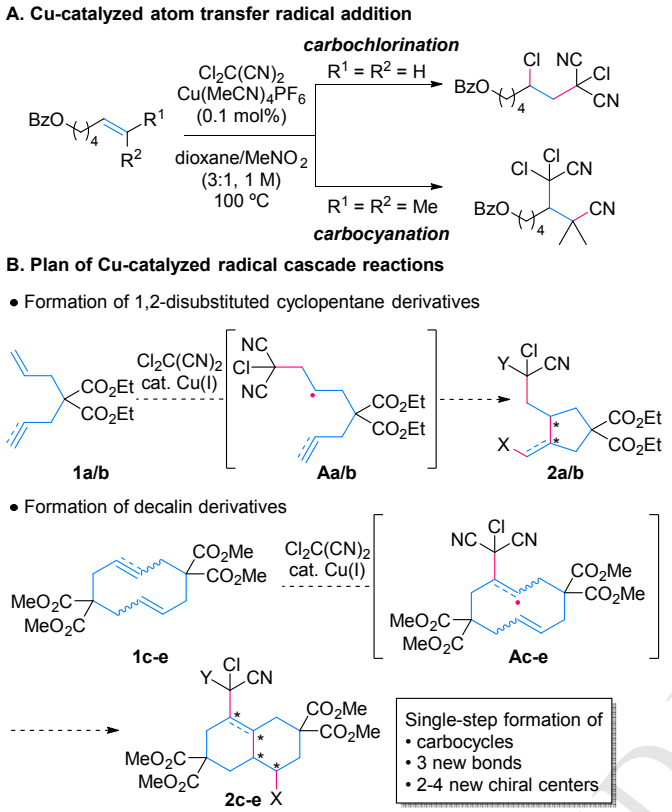
We were interested in expanding the scope of the Cu-catalyzed radical reaction of $Cl_2C(CN)_2$, and aimed to realize radical-based cascade reactions by combining olefin addition with ring formation (Scheme 1B). Accordingly, we designed five unsaturated substrates **1a**-**e** that differed in unsaturation and topology. Diene **1a** and enyne **1b** are linear compounds, while dienes **1c**/**d** and enyne **1e** possess 10-membered carbocycles. We envisioned that **1a/b** and **1c-e** would be converted to the 1,2-disubstituted cyclopentane derivatives **2a/b** and the decalin derivatives **2c-e** through radical intermediates **Aa/b** and **Ac-e**, respectively.[6] Although it was unclear at this stage whether carbochlorination or carbocyanation was the preferred pathway for the transformations, these reactions would generate the functionalized carbocycles from the simple unsaturated compounds by forming the three new bonds and multiple chiral centers.[7] Here we report development of such Cu-catalyzed radical cascade reactions for the assembly of four different products, and provide the rationale for their chemo- and stereoselectivities.

2. Results and discussion

2-1. Synthesis of 10-membered compounds 1c-e

Whereas linear precursors **1a** and **1b** are commercially available, the three 10-membered substrates **1c-e** required synthetic preparation. Therefore, *E*,*E*-diene **1c**, *Z*,*Z*-diene **1d**, and enyne **1e** were constructed via a series of alkylations from *Z*-olefin **3** according to the procedure developed by Deslongchamps (Scheme 2).[8] PCC oxidation of alcohol **3** provided the α,β-unsaturated aldehyde, the *Z*-olefin of which was isomerized in situ into the corresponding *E*-isomer **4**. After 1,2-reduction of enal **4** with DIBAL-H, the hydroxy group of **5** was converted into chloride using the reagent combination of MsCl and LiCl. Allyl chloride **6** was then subjected to S_N2 displacement with dimethyl malonate (**7**) under basic conditions to provide **8**. The four-

carbon unit was installed by the reaction of **8** with (*E*)-1,4-dichloro-2-butene (**9a**) and K_2CO_3. The allylic chloride of the thus-obtained **10** was used as the leaving group in the second displacement with **7**, affording **11**. Acid hydrolysis of the THP group of **11** and chlorination of the resultant hydroxy group of **12** gave rise to **13**. K_2CO_3-induced cyclization of allyl chloride **13** was effected in the presence *n*-Bu_4NI under high dilution conditions (1 mM) to furnish the 10-membered compound **1c** with the *E*,*E*-diene in 40% yield.



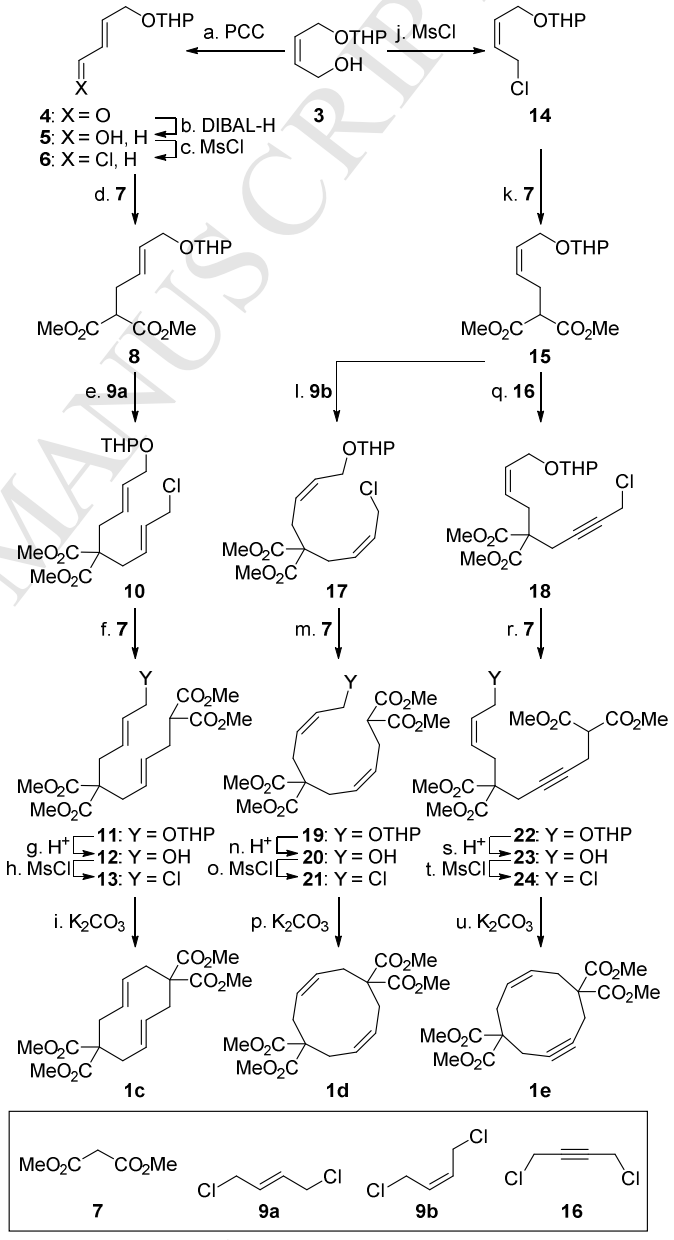
Scheme 1. (**A**) Previously reported Cu-catalyzed atom transfer radical addition of $Cl_2C(CN)_2$, and (**B**) plan for synthesis of the 1,2-disubstituted cyclopentane and decalin derivatives by the Cu-catalyzed radical cascade reactions.

Z,*Z*-diene **1d** was prepared from the same starting material **3** by applying a similar reaction sequence. After the hydroxy group of **3** was chlorinated, the allylic chloride was displaced with **7** to provide **15**. The next carbon chain extension using (*Z*)-1,4-dichloro-2-butene (**9b**) transformed **15** to *Z*,*Z*-diene **17**. The obtained **17** was subjected to the same four-step transformations from *E*,*E*-diene **10** to **1c**, yielding 10-membered compound **1d** with the *E*,*E*-diene.

The intermediate **15** was employed for the synthesis of enyne **1e**. Compound **15** was coupled with 1,4-dichloro-2-butyne (**16**) under basic conditions to afford **18**, which was further homologated with **7** to produce **22**. THP-ether **22** was then converted to chloride **24** by acid hydrolysis and subsequent chlorination. Formation of the 10-membered ring from **24** was realized by base-induced intramolecular S_N2 displacement under high dilution conditions, generating enyne **1e**.

2-2. Cu-catalyzed conversion from 1a/b to 1,2-disubstituted cyclopentane derivatives 2a/b

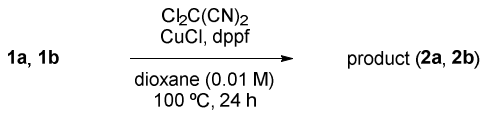
The Cu-catalyzed radical cascade reactions were first explored using linear diene **1a** and enyne **1b** (Table 1). Both substrates were separately treated with $Cl_2C(CN)_2$ (5 equiv) in the presence of catalytic amounts of CuCl (3 mol%) and 1,1'-bis(diphenylphosphino)ferrocene (dppf, 3 mol%) in refluxing dioxane (0.01 M).[9] The reaction of diene **1a** stereoselectively proceeded under these conditions to provide a 6 : 1 mixture of *cis*-isomer **2a** and its *trans*-isomer in 95% combined yield (entry 1). Enyne **1b** also functioned as the precursor of the desired transformation under the same conditions, furnishing **2b** as the sole stereoisomer in 67% yield (entry 2). In both cases, addition of chloromalononitrile radicals occurred at the olefin of **1a** and **1b**, and subsequently resulted in the formation of the 1,5-dicyanated products **2a** and **2b**. Reflecting the intrinsically higher reactivity of alkenes than alkynes toward radicals,[10] the alkene of **1b** chemoselectively reacted with chloromalononitrile radicals over its alkyne, and the intramolecular migration of the CN group occurred prior to the intermolecular chlorination in the generation of **2a** and **2b**.[11]

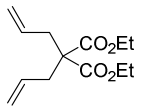
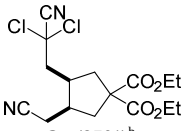
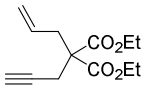
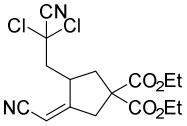


Scheme 2. Syntheses of 10-membered compounds **1c-e**. Reagents and conditions: (a) PCC, NaOAc, CH_2Cl_2; (b) DIBAL-H, CH_2Cl_2, 62% (2 steps); (c) LiCl, MsCl, 2,4,6-collidine, DMF; (d) **7**, K_2CO_3, MeCN, 90 ˚C, 78% (2 steps); (e) **9a**, K_2CO_3, MeCN, 90 ˚C, 80%; (f) **7**, K_2CO_3, MeCN, 90 ˚C, 71%; (g) (+)-CSA, MeOH; (h) LiCl, MsCl, 2,4,6-collidine, DMF, 69% (2 steps); (i) K_2CO_3, *n*-Bu_4NI, MeCN, 90 ˚C, 40%; (j) LiCl, MsCl, 2,4,6-collidine, DMF; (k) **7**, K_2CO_3, MeCN, 90 ˚C, 64% (2 steps); (l) **9b**, K_2CO_3, MeCN, 90 ˚C, 76%; (m) **7**, K_2CO_3, MeCN, 90 ˚C; (n) (+)-CSA, MeOH, 70% (2 steps); (o) LiCl, MsCl, 2,4,6-collidine, DMF, 81%; (p) K_2CO_3, *n*-Bu_4NI, MeCN, 90 ˚C, 70%; (q) **16**, K_2CO_3, MeCN, 90 ˚C, 78%; (r) **7**, K_2CO_3, MeCN, 90 ˚C, 85%; (s) PPTS, MeOH, 83%; (t) LiCl, MsCl, 2,4,6-collidine, DMF; (u) K_2CO_3, *n*-

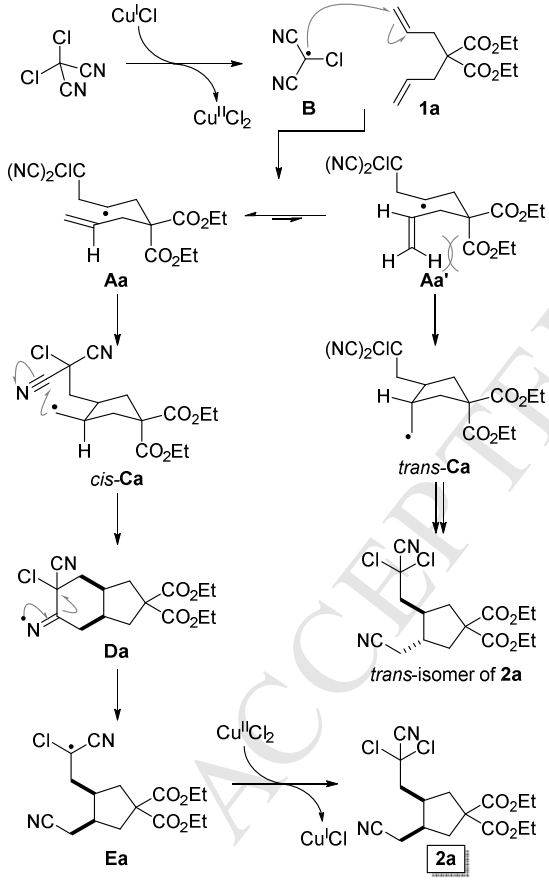
Bu_4NI, MeCN, 90 ˚C, 79% (2 steps). CSA = 10-camphorsulfonic acid, DIBAL-H = diisobutylaluminium hydride, MsCl = methanesulfonyl chloride, PCC = pyridinium chlorochromate, PPTS = pyridinium *p*-toluenesulfonate, THP = 2-tetrahydropyranyl.

Table 1. Cu-catalyzed radical cascade reactions of **1a**/**b**.[a]



Entry	1a, 1b	Results
1	 **1a**	 **2a** (95%)[b]
2	 **1b**	 **2b** (67%)

[a]Reagents and conditions: $Cl_2C(CN)_2$ (5 equiv), CuCl (3 mol%), 1,1'-bis(diphenylphosphino)ferrocene (dppf, 3 mol%), dioxane (0.01 M), 100 °C, 24 h; [b]A 6 : 1 mixture of **2a** and the *trans*-isomer of **2a** was obtained.



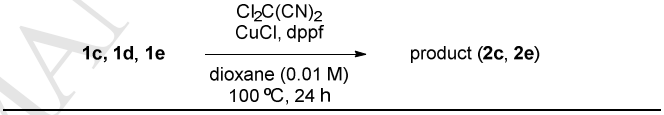
Scheme 3. The radical cascade pathway for the formation of cyclopentane derivative **2a** from **1a**.

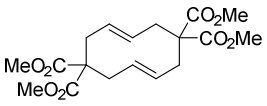
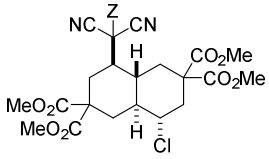
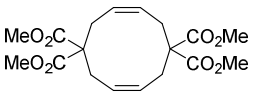
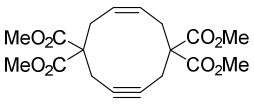
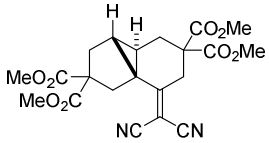
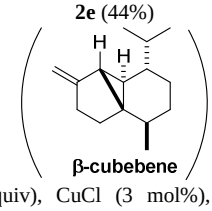
Scheme 3 illustrates the plausible radical cascade process from **1a** to **2a**. Cu(I)Cl homolytically cleaves a C–Cl bond of $Cl_2C(CN)_2$ at 100 °C to generate chloromalononitrile radical **B** and $Cu(II)Cl_2$.[12] **B** in turn reacts with the double bond of **1a**, and the resultant **Aa** undergoes 5-*exo*-*trig*-cyclization. **Aa** is more concentrated than its conformational isomer **Aa'**, which has an unfavorable steric interaction between the olefinic hydrogen and CO_2Et group. Thus, formation of *cis*-**Ca** from **Aa** is preferred over that of *trans*-**Ca** from **Aa'**. Presumably due to the relatively slow intermolecular chlorination of **Ca**, *cis*-**Ca** intramolecularly adds to the C–N triple bond, generating the 6-membered iminyl radical **Da**. The unstable iminyl radical undergoes cleavage of the C–C bond to give the more stable **Ea**, whose radical is delocalized to the CN and Cl groups. After this 1,5-cyanide transfer, radical **Ea** is chlorinated with $Cu(II)Cl_2$, and the 1,5-dicyanated adduct **2a** is formed as the final product with regeneration of the Cu(I)Cl catalyst. The minor *trans*-isomer of **2a** is produced in a similar fashion from *trans*-**Ca**. When **1b** is employed instead of **1a**, cyanide migration occurs from the sp^3-carbon to the sp^2-carbon, leading to vinyl cyanide **2b**.

2-3. Cu-catalyzed conversion from 1c-e to *trans*-decalin derivatives 2c-e

Next, the Cu-catalyzed atom transfer radical addition was applied to the three 10-membered substrates **1c-e** (Table 2). Upon heating *E*,*E*-diene **1c** with CuCl (3 mol%), dppf (3 mol%) and $Cl_2C(CN)_2$ (5 equiv) in dioxane at 100 °C, *trans*-decalin **2ca** was obtained in 46% yield along with the minor product **2cb** in 16% yield (entry 1). The formation of 1,5-dichlorinated compound **2ca** as the major product indicates that cyanide migration did not occur in this case. Most importantly, the single operation permitted the three bonds to link and the four contiguous stereocenters to be installed.

Table 2. Cu-catalyzed radical cascade reactions of **1c-e**.[a]



Entry	1c-e	Results
1	 **1c**	 **2ca**: Z = Cl (46%) **2cb**: Z = H (16%)
2	 **1d**	no reaction[b]
3	 **1e**	 **2e** (44%)
		 **β-cubebene**

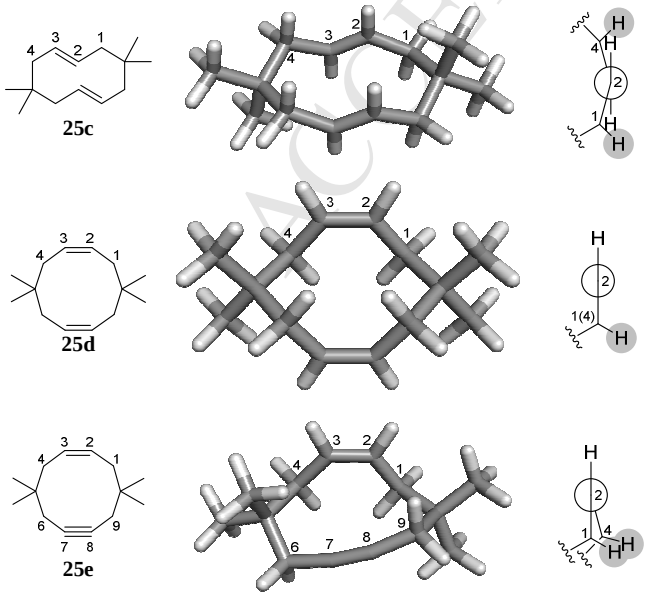
[a]Reagents and conditions: $Cl_2C(CN)_2$ (5 equiv), CuCl (3 mol%), 1,1'-bis(diphenylphosphino)ferrocene (dppf, 3 mol%), dioxane (0.01 M), 100 °C, 24 h; [b]**1d** was recovered in 93% yield

Intriguingly, *Z*,*Z*-diene **1d**, the stereoisomer of *E*,*E*-diene **1c**, was inert to the Cu-catalyzed conditions, resulting in the recovery of only the starting material **1d** (93%, entry 2). The contrasting results of entries 1 and 2 revealed the significantly lower reactivity of the *Z*-alkene of **1d** compared to the *E*-alkene of **1c** toward chloromalononitrile radical **B**.

When enyne **1e** with the *Z*-alkene and alkyne was submitted to the radical reaction (entry 3), fused tricycle **2e** was formed from **1e** in 44% yield as the sole detectable product. In this reaction, **B** first added to the alkyne moiety due to the low reactivity of the *Z*-alkene, and subsequent multiple bond formations afforded **2e** without the cyanide transfer (vide supra). Consequently, the observed chemoselectivity between the alkene and alkyne was switched from that of acyclic **1b** (Table 1, entry 2), where the double bond reacted to **B** in the presence of the triple bond. Overall, the reaction from the simple 10-membered compound **1** attained the construction of the ring system of a natural product, β-cubebene, in one step,[13] demonstrating the high efficiency of the transformation for generating the intricately fused architecture.

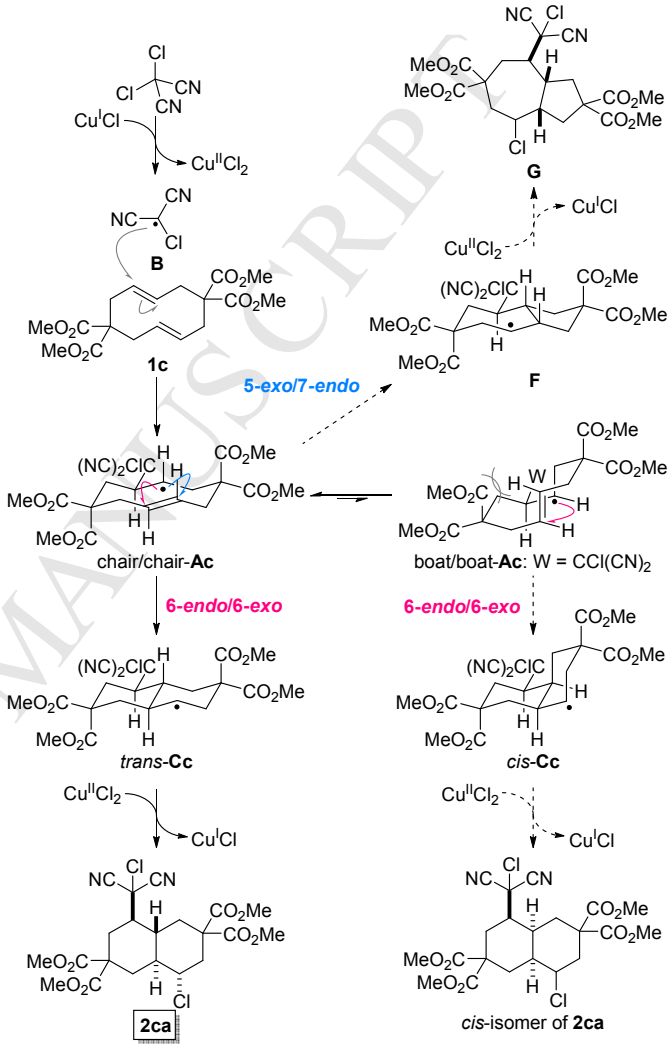
To rationalize the first radical addition of the chloromalononitrile radicals to **1c-e**, the most stable three-dimensional structures of the 10-membered compounds were computationally analyzed (Table 3). To facilitate the calculation, the methoxy carbonyl groups of **1c-e** were simplified to the methyl groups of **25c-e**. Compounds **25c-e** were submitted to the DFT calculation at the M06-2X/6-31g(d) level of theory (289 K, 1 atm) to generate their most stable conformers.[14] The allylic C1-H and C4-H of **25c-e** are orthogonal to the double bonds, thereby sterically shielding the olefins from the radical addition. The kinetic protection effect of the allylic protons is attributable to the negligible reactivity of **1d** and the chemoselectivity toward the less hindered alkyne of **1e**. On the other hand, the higher reactivity of the *E*-olefin of **1c** than the *Z*-olefin of **1d** can be explained by the more distorted nature of the *E*-olefin compared with the *Z*-olefin. The dihedral angles of C1–C2–C3–C4 (163.8°), H2-C2-C3-C4 (-7.6°), and C1-C2-C3-H3 (-7.6°) of **25c** indicated a significant deviation from the ideal π-bond plane compared to those of C1–C2–C3–C4 (0.0°), H2-C2-C3-C4 (179.0°), and C1-C2-C3-H3 (-179.0°) of **25d**. Thus, the radicals readily react with the twisted π-bond of **1c**, but not with the planar π-bond of **1d**.[15,16] The bended triple bond [C6-C7-C8-C9 (-7.1°)] within the 10-membered ring of **25e** is also likely due to the chemoselective reaction at the alkyne site of **1e**. Therefore, the observed reactivities and chemoselectivities of the addition reactions to **1c-e** would come from the steric effects of the allylic protons and the distortion magnitudes of the unsaturated bonds.

Table 3. Computed 10-membered rings **25c-e**, their Newman projection, and the calculated data of the dihedral and bond angles.



	Dihedral angles (deg)				
	C1-C2-C3-C4	H2-C2-C3-H3	H2-C2-C3-C4	C1-C2-C3-H3	C6-C7-C8-C9
25c	163.8	-178.9	-7.6	-7.6	–
25d	0.0	0.0	179.0	-179.0	–
25e[a]	-5.4	-0.2	175.7	178.7	-7.1

[a]Bond angles (deg): θ(C6-C7-C8) = 170.3, θ(C7-C8-C9) = 167.7.

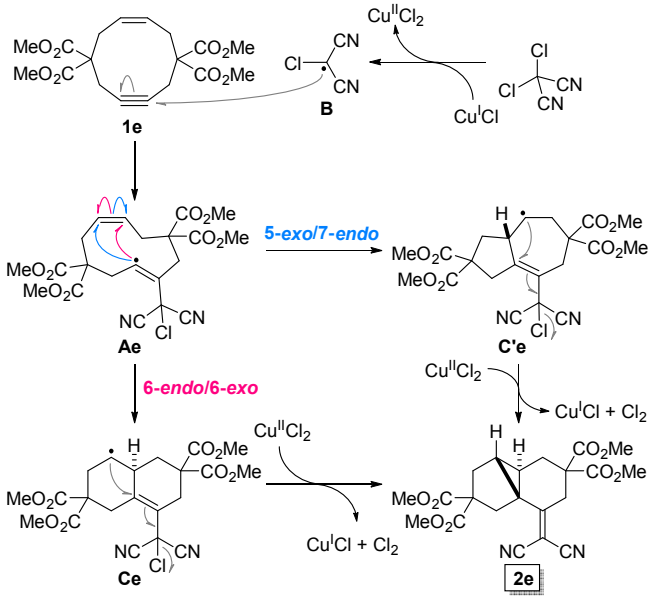


Scheme 4. The radical cascade reaction for the formation of *trans*-decalin **2ca** from **1c**.

The reaction pathways of the cascade radical reactions from **1c** to **2ca** and from **1e** to **2e** are proposed in Schemes 4 and 5, respectively. Cu(I)Cl induces conversion of $Cl_2C(CN)_2$ into **B** via homolytic cleavage of the C-Cl bond (Scheme 4). The radical addition of **B** to the *E*-alkene of **1c** produces chair/chair-**Ac** or boat/boat-**Ac**. The selective formation of **2ca** over those of **G** and the *cis*-isomer of **2ca** would originate from the relative stability of the radical intermediates. As the conformer boat/boat-**Ac** has an unfavorable steric interaction, the reaction would not go through the boat/boat-**Ac** that leads to *cis*-**Cc**. The 6-*endo*/6-*exo* and 5-*exo*/7-*endo* transannular reactions from chair/chair-**Ac** deliver the 6/6-ring system *trans*-**Cc** and 5/7-ring system **F**, respectively. Although the formation of 5-membered ring **F** can be predicted on the basis of the acyclic precedent (**1a** →*cis*-**Ca**→**2a**), **G** was not isolated in this reaction. This is probably because less thermodynamically stable **F** is equilibrated into more stable decalin *trans*-**Cc** before termination of the

secondary radical **F** to produce **G**.[17] Finally, because the alkyl radical of *trans*-**Cc** cannot add to the CN group of the equatorially-oriented $ClC(CN)_2$ group in an intramolecular manner, $Cu(II)Cl_2$ intermolecularly chlorinates *trans*-**Cc** from the less hindered α-face of the decalin, affording **2ca**. Hydrogen abstraction of *trans*-**Cc** would in turn give minor product **2cb**.

The bended triple bond of **1e** reacts with radical **B** to generate vinyl radical **Ae** (Scheme 5). The 6-*endo*/6-*exo* and 5-*exo*/7-*endo* transannular reactions of **Ae** give the two different intermediates **Ce** and **C'e**, respectively, which can converge into the same product **2e** via the second cyclization through an S_H2' reaction. In both cases, the eliminated chloro radicals would react with $Cu(II)Cl_2$ to regenerate Cu(I)Cl and produce Cl_2.



Scheme 5. Two possible pathways for the formation of **2e** from 10-membered compound **1e**.

3. Conclusions

In summary, a Cu-catalyzed atom transfer radical addition of $Cl_2C(CN)_2$ was employed to convert acyclic **1a** and **1b**, and 10-membered **1c** and **1e** into four different ring structures, **2a**, **2b**, **2c** and **2e**, respectively. Under these conditions, the intramolecular CN-transfer occurred to generate 1,5-dicyanated products **2a** and **2b**, while the intermolecular Cl-transfer afforded 1,5-dichlorinated product **2c**, and the radical Cl-ejection gave rise to **2e**. Formation of the tricyclic structure of β-cubebene from **1e** particularly demonstrates the high efficiency of the present radical cascade reaction for increasing the molecular complexity in a single step. Analyses of the chemo- and stereoselectivities of the cyclization reactions revealed that the enhanced reactivities of the *E*-olefin of **1c** and the alkyne of **1e** were attributable to their strained characters. Since the installed functional groups on the carbocycles can be used as a handle for further functionalization,[3] the present method offers a new entry for concise preparation of functional materials, pharmaceuticals, and natural products with carbocyclic motifs.

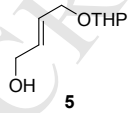
4. Experimental section

4.1. General method

All reactions were carried out under argon atmosphere in dry solvents. CH_2Cl_2 and DMF were purified by Glass Contour solvent dispensing system (Nikko Hansen & Co., Ltd.). All other reagents were used as supplied. Analytical thin-layer chromatography (TLC) was performed using E. Merck Silica gel 60 F254 pre-coated plates, 0.25 mm. Flash chromatography was performed using 40-50 μm Silica Gel 60N (Kanto Chemical Co., Inc.). Infrared (IR) spectra were recorded on JASCO FT-IR-4100 spectrometer. ^1H and ^{13}C NMR spectra were recorded on JEOL JNM-ECX-500, JNM-ECA-500, or JNM-ECS-400 spectrometer. Chemical shifts were reported in ppm on the δ scale relative to $CHCl_3$ (δ = 7.26 for ^1H NMR), $CDCl_3$ (δ = 77.0 for ^{13}C NMR), C_6D_5H (δ = 7.16 for ^1H NMR), C_6D_6 (δ = 128.0 for ^{13}C NMR), CD_2HOD (δ = 3.31 for ^1H NMR) and CD_2HCN (δ = 1.94 for ^1H NMR) as internal references. Signal patterns are indicated as s, singlet; d, doublet; t, triplet; m; multiplet. High resolution mass spectra were measured on JEOL JMS-T100LP instrument.

4.2. Synthesis of *E,E*-diene 1c

4.2.1. Allyl alcohol 5 [CAS: 77741-47-0][8b]

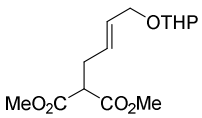


5

Allyl alcohol **3** (8.50 g, 49.4 mmol) in CH_2Cl_2 (85 mL) was added to a solution of PCC (16.0 g, 74.1 mmol) and NaOAc (1.21 g, 14.8 mmol) in CH_2Cl_2 (80 mL). The reaction mixture was stirred for 2 h at room temperature, and then Et_2O (50 mL) was added. The solution was passed through a short pad of florisil (50 g) with Et_2O (100 mL). The filtrate was concentrated to afford the crude enal **4** (5.40 g), which was used in the next reaction without further purification.

DIBAL-H (1.0 M in *n*-hexane, 64.0 mL, 64.0 mmol) was added to a solution of the above crude **4** (5.40 g) in CH_2Cl_2 (160 mL) at 0 ºC. After the reaction mixture was stirred for 30 min at room temperature, the reaction was quenched with saturated aqueous Rochelle's salt (100 mL) and MeOH (15 mL) at 0 ºC. The resultant mixture was stirred for 10 h at room temperature and extracted with EtOAc (100 mL×2). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash chromatography on silica gel (100 g, *n*-hexane/EtOAc 4/1 to 2/1) to afford allyl alcohol **5** (5.27 g, 30.6 mmol) in 62% yield over 2 steps.

4.2.2. Diester 8 [CAS: 93915-02-7][8b]



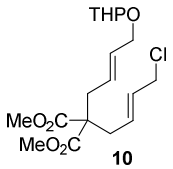
8

2,4,6-Collidine (4.20 mL, 31.8 mmol) and LiCl (1.23 g, 28.9 mmol) were added to a solution of allyl alcohol **5** (4.98 g, 28.9 mmol) in DMF (30 mL) at 0 ºC. After the reaction mixture was stirred for 15 min at 0 ºC, MsCl (2.46 mL, 31.8 mmol) was added dropwise to the mixture. The reaction mixture was then stirred for 1 h at room temperature. The reaction was quenched with H_2O (30 mL) at 0 ºC, and the resultant mixture was extracted with Et_2O (30 mL×2). The combined organic layers were washed with saturated aqueous $Cu(NO_3)_2$ (30 mL), dried over Na_2SO_4, filtered, and concentrated to afford the crude chloride **6** (5.50 g), which was used in the next reaction without further purification.

Dimethylmalonate (**7**) (3.95 mL, 34.7 mmol) was added to a solution of the above crude **6** (5.50 g) and K_2CO_3 (7.99 g, 57.8 mmol) in MeCN (300 mL) at room temperature. The reaction mixture was stirred for 20 h at 90 ºC, and then H_2O (100 mL) was added at 0 ºC. The resultant mixture was extracted with

Et_2O (100 mL×3), and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography on silica gel (100 g, *n*-hexane/EtOAc 4/1) to afford diester **8** (6.47 g, 22.6 mmol) in 78% yield over 2 steps.

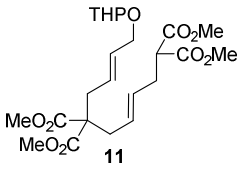
4.2.3. Chloride 10 [CAS: 112181-18-7][8b]



10

(*E*)-1,4-Dichloro-2-butene (**9a**) (1.35 mL, 12.3 mmol) was added to a solution of diester **8** (705 mg, 2.46 mmol) and K_2CO_3 (1.36 g, 9.84 mmol) in MeCN (26 mL) at room temperature. The reaction mixture was stirred for 12 h at 90 ºC, and then H_2O (30 mL) was added at 0 ºC. The resultant mixture was extracted with Et_2O (30 mL×3), and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography on silica gel (30 g, *n*-hexane/EtOAc 4/1) to afford chloride **10** (737 mg, 1.97 mmol) in 80% yield.

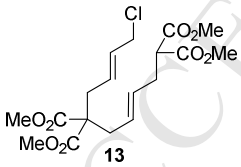
4.2.4. Tetraester 11 [CAS: 112181-19-8][8b]



11

Dimethylmalonate (**7**) (897 μL, 7.88 mmol) was added to a solution of chloride **10** (737 mg, 1.97 mmol) and K_2CO_3 (544 mg, 3.94 mmol) in MeCN (20 mL) at room temperature. The reaction mixture was stirred for 12 h at 90 ºC, and then H_2O (20 mL) was added at 0 ºC. The resultant mixture was extracted with Et_2O (20 mL×3), and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography on silica gel (30 g, *n*-hexane/EtOAc 4/1 to 2/1) to afford tetraester **11** (656 mg, 1.39 mmol) in 71% yield.

4.2.5. Chloride 13 [CAS: 93915-04-9][8b]

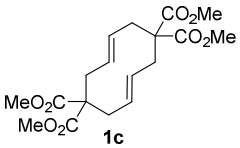


13

(+)-CSA (32.3 mg, 139 μmol) was added to a solution of tetraester **11** (656 mg, 1.39 mmol) in MeOH (6.5 mL). After being stirred for 2 h at room temperature, the reaction mixture was concentrated. The residue was dissolved in EtOAc (10 mL). The resultant mixture was washed with saturated aqueous $NaHCO_3$ (5 mL), dried over Na_2SO_4, filtered, and concentrated to afford the crude allyl alcohol **12** (600 mg), which was used in the next reaction without further purification.

2,4,6-Collidine (202 μL, 1.53 mmol) and LiCl (58.9 mg, 1.39 mmol) were added to a solution of the above crude **12** (600 mg) in DMF (1.5 mL) at 0 ºC. After the reaction mixture was stirred for 15 min at 0 ºC, MsCl (118 μL, 1.53 mmol) was added. The reaction mixture was then stirred for 1 h at room temperature. The reaction was quenched with H_2O (2 mL) at 0 ºC, and the resultant mixture was extracted with Et_2O (2 mL×2). The combined organic layers were washed with saturated aqueous $Cu(NO_3)_2$ (5 mL), dried over Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography on silica gel (5 g, *n*-hexane/EtOAc 4/1) to afford chloride **13** (387 mg, 95.9 μmol) in 69% yield over 2 steps.

4.2.6. *E,E*-Diene 1c [CAS: 93915-10-7][8b]

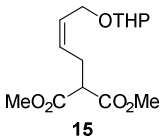


1c

K_2CO_3 (661 mg, 4.78 mmol) and *n*-Bu_4NI (1.41 g, 3.82 mmol) were added to a solution of chloride **13** (387 mg, 959 μmol) in MeCN (190 mL) at room temperature. The reaction mixture was stirred for 12 h at 90 ºC and concentrated. The residue was dissolved in Et_2O (20 mL). The resultant mixture was washed with H_2O (20 mL), dried over Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography on silica gel (10 g, *n*-hexane/EtOAc 4/1) to afford 10-membered ring **1c** (140 mg, 382 μmol) in 40% yield.

4.3. Synthesis of *Z,Z*-diene 1d

4.3.1. Diester 15 [CAS: 104951-13-5][8b]

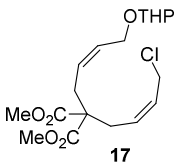


15

2,4,6-Collidine (645 μL, 4.88 mmol) and LiCl (207 mg, 4.88 mmol) were added to a solution of allyl alcohol **3** (764 mg, 4.44 mmol) in DMF (2.2 mL) at 0 ºC. After the reaction mixture was stirred for 15 min at 0 ºC, MsCl (378 μL, 4.88 mmol) was added. The reaction mixture was then stirred for 1 h at room temperature. The reaction was quenched with H_2O (2 mL) at 0 ºC, and the resultant mixture was extracted with Et_2O (2 mL×2). The combined organic layers were washed with saturated aqueous $Cu(NO_3)_2$ (2 mL), dried over Na_2SO_4, filtered, and concentrated to afford the crude chloride **14** (1.10 g), which was used in the next reaction without further purification.

Dimethylmalonate (**7**) (765 μL, 6.66 mmol) was added to a solution of the above crude **14** (1.10 g) and K_2CO_3 (3.07 g, 22.2 mmol) in MeCN (4.4 mL) at room temperature. The reaction mixture was stirred for 25 h at 90 ºC, and then concentrated. The residue was dissolved in Et_2O (3 mL). The resultant mixture was washed with H_2O (3 mL), and the aqueaous layer was extracted with Et_2O (3 mL×2). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography on silica gel (10 g, *n*-hexane/EtOAc 4/1) to afford diester **15** (810 mg, 2.83 mmol) in 64% yield over 2 steps.

4.3.2. Chloride 17

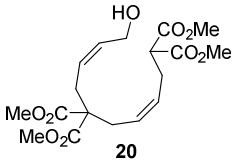


17

(*Z*)-1,4-Dichloro-2-butene (**9b**) (1.80 mL, 17.1 mmol) was added to a solution of malonate **15** (2.72 g, 9.50 mmol) and K_2CO_3 (6.56 g, 47.5 mmol) in MeCN (48 mL) at room temperature. The reaction mixture was stirred for 12 h at 90 ºC, and then H_2O (30 mL) was added at 0 ºC. The resultant mixture was extracted with Et_2O (30 mL×3), and the combined organic

layers were dried over Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography on silica gel (30 g, *n*-hexane/EtOAc 4/1) to afford chloride **17** (2.71 g, 7.22 mmol) in 76% yield: IR (film) 2951, 2869, 1733, 1438, 1202, 1026 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.51-1.60 (4H, m, $OCH_2CH_2CH_ACH_A$), 1.71 (1H, m, $OCH_2CH_2CH_BCH_2$), 1.81 (1H, m, $OCH_2CH_2CH_2CH_B$), 2.71 (4H, dd, *J* = 7.8, 1.4 Hz, H4, 6), 3.51 (1H, m, $OCH_ACH_2CH_2CH_2$), 3.72 (6H, s, CO_2CH_3 ×2), 3.86 (1H, m, $OCH_BCH_2CH_2CH_2$), 4.01-4.27 (4H, m, H1, 9), 4.61 (1H, dd, *J* = 3.4, 3.4 Hz, OC*H*O), 5.67-5.78 (4H, m, H2, 3, 7, 8); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.4, 25.4, 30.2, 30.6, 30.8, 38.9, 52.7 (2C), 57.2, 62.2, 62.7, 98.2, 125.6, 127.6, 129.2, 130.6, 171.0 (2C); HRMS (ESI) calcd for $C_{18}H_{27}ClO_6Na$ $[M+Na]^+$ 397.1388, found 397.1396.

4.3.3. Allyl alcohol 20 [CAS: 112181-15-4][8b]

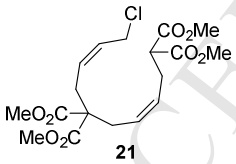


20

Dimethylmalonate (**7**) (3.17 mL, 27.8 mmol) was added to a solution of chloride **17** (2.61 g, 6.96 mmol) and K_2CO_3 (1.92 g, 13.9 mmol) in MeCN (35 mL) at room temperature. The reaction mixture was stirred for 12 h at 90 ºC, and then H_2O (20 mL) was added at 0 ºC. The resultant mixture was extracted with Et_2O (20 mL×3), and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated to afford the crude tetraester **19** (3.50 g), which was used in the next reaction without further purification.

(+)-CSA (162 mg, 696 μmol) was added to a solution of the above crude **19** (3.50 g) in MeOH (70 mL). After being stirred for 2 h at room temperature, the reaction mixture was concentrated. The residue was dissolved in EtOAc (10 mL). The resultant mixture was washed with saturated aqueous $NaHCO_3$ (10 mL), dried over Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography on silica gel (50 g, *n*-hexane/EtOAc 2/1) to afford allyl alcohol **20** (1.88 g, 4.92 mmol) in 70% yield over 2 steps.

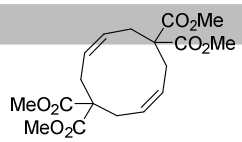
4.3.4. Chloride 21 [CAS: 93915-07-2][8b]



21

2,4,6-Collidine (153 μL, 1.16 mmol) and LiCl (49.0 mg, 1.16 mmol) were added to a solution of allyl alcohol **20** (400 mg, 1.05 mmol) in DMF (2.2 mL) at 0 ºC. After the reaction mixture was stirred for 15 min at 0 ºC, MsCl (89.6 μL, 1.16 mmol) was added. The reaction mixture was then stirred for 1 h at room temperature. The reaction was quenched with H_2O (3 mL) at 0 ºC, and the resultant mixture was extracted with Et_2O (3 mL×2). The combined organic layers were washed with saturated aqueous $Cu(NO_3)_2$ (5 mL), dried over Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography on silica gel (5 g, *n*-hexane/EtOAc 4/1) to afford chloride **21** (348 mg, 859 μmol) in 81% yield.

4.3.5. *Z,Z*-Diene 1d [CAS: 93915-08-3][8b]

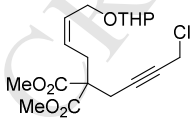


1d

K_2CO_3 (607 mg, 4.39 mmol) and *n*-Bu_4NI (1.22 g, 3.30 mmol) were added to a solution of chloride **21** (348 mg, 859 μmol) in MeCN (220 mL) at room temperature. After being stirred for 12 h at 90 ºC, the reaction mixture was concentrated. The residue was dissolved in Et_2O (10 mL). The resultant mixture was washed with H_2O (5 mL), dried over Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography on silica gel (10 g, *n*-hexane/EtOAc 4/1) to afford 10-membered ring **1d** (222 mg, 603 μmol) in 70% yield.

4.4. Synthesis of enyne 1e

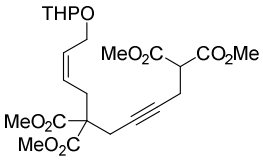
4.4.1. Chloride 18 [CAS: 112181-12-1][8b]



18

1,4-Dichloro-2-butyne (**16**) (1.26 mL, 13.1 mmol) was added to a solution of malonate **15** (2.50 g, 8.73 mmol) and K_2CO_3 (3.62 g, 26.2 mmol) in MeCN (60 mL) at room temperature. The reaction mixture was stirred for 12 h at 90 ºC, and then H_2O (30 mL) was added at 0 ºC. The resultant mixture was extracted with Et_2O (30 mL×3), and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography on silica gel (30 g, *n*-hexane/EtOAc 4/1) to afford chloride **18** (2.54 g, 6.81 mmol) in 78% yield.

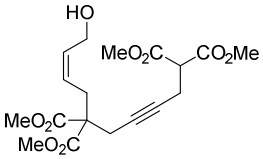
4.4.2. Tetraester 22 [CAS: 112181-13-2][8b]



22

Dimethylmalonate (**7**) (3.19 mL, 27.2 mmol) was added to a solution of chloride **18** (2.54 g, 6.81 mmol) and K_2CO_3 (1.88 g, 13.6 mmol) in MeCN (35 mL) at room temperature. The reaction mixture was stirred for 12 h at 90 ºC, and then H_2O (20 mL) was added at 0 ºC. The resultant mixture was extracted with Et_2O (20 mL×3), and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography on silica gel (30 g, *n*-hexane/EtOAc 4/1) to afford tetraester **22** (2.71 g, 6.81 mmol) in 85% yield.

4.4.3. Allyl alcohol 23 [CAS: 112181-14-3][8b]

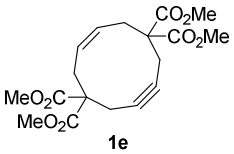


23

PPTS (171 mg, 681 μmol) was added to a solution of tetraester **22** (2.71 g, 6.81 mmol) in MeOH (70 mL). After being stirred for 2 h at room temperature, the reaction mixture was concentrated. The residue was dissolved in EtOAc (10 mL). The

resultant mixture was washed with saturated aqueous $NaHCO_3$ (10 mL), dried over Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography on silica gel (50 g, *n*-hexane/EtOAc 2/1) to afford allyl alcohol **23** (2.17 g, 5.65 mmol) in 83% yield.

4.4.4. Enyne 1e [CAS: 93915-11-8][8b]



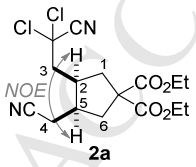
1e

2,4,6-Collidine (715 μL, 5.41 mmol) and LiCl (209 mg, 4.92 mmol) were added to a solution of allyl alcohol **23** (1.89 g, 4.92 mmol) in DMF (9.5 mL) at 0 ºC. After the reaction mixture was stirred for 15 min at 0 ºC, MsCl (418 μL, 5.41 mmol) was added. The reaction mixture was then stirred for 1 h at room temperature. The reaction was quenched with H_2O (10 mL) at 0 ºC, and the resultant mixture was extracted with Et_2O (10 mL×2). The combined organic layers were washed with saturated aqueous $Cu(NO_3)_2$ (10 mL), dried over Na_2SO_4, filtered, and concentrated to afford the crude chloride **24** (2.10 g), which was used in the next reaction without further purification.

K_2CO_3 (2.04 g, 14.8 mmol) and *n*-Bu_4NI (3.63 g, 9.84 mmol) were added to a solution of the above crude **24** (2.10 g) in MeCN (330 mL) at room temperature. After being stirred for 16 h at 90 ºC, the reaction mixture was concentrated. The residue was dissolved in Et_2O (10 mL). The resultant mixture was washed with H_2O (5 mL), dried over Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography on silica gel (20 g, *n*-hexane/EtOAc 4/1) to afford 10-membered ring **1e** (1.42 g, 3.89 mmol) in 79% yield over 2 steps.

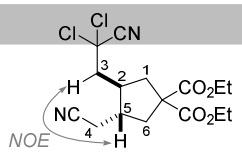
4.5. General procedure: synthesis of carbocycle 2a

Diene **1a** (24.0 mg, 0.100 mmol) and $Cl_2C(CN)_2$ (50.0 μL, 0.500 mmol) were added to a solution of CuCl (0.30 mg, 3.0 μmol) and 1,1'-bis(diphenylphosphino)ferrocene (dppf, 1.60 mg, 3.00 μmol) in dioxane (10.0 mL). The mixture was degassed by freeze-thaw for three times, purged with Ar, and stirred at 100 ˚C for 24 h. The reaction mixture was then filtered through a pad of silica gel (1 g, Et_2O), and the filtrate was concentrated. The residue was purified by a flash column chromatography on silica gel (1 g, hexane/EtOAc 10:1 to 3:1) to give carbocycle **2a** (30.5 mg, 81.2 μmol), and the *trans*-isomer of **2a** (5.08 mg, 13.5 μmol) in 81%, and 14% yields, respectively.



2a

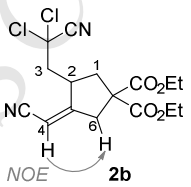
2a: yellow oil; IR (film) 2360, 1727, 1261 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 0.88 (3H, t, *J* = 7.3 Hz, $CO_2CH_2CH_3$), 0.92 (3H, t, *J* = 7.3 Hz, $CO_2CH_2CH_3$), 1.18 (1H, dd, *J* = 16.3, 5.0 Hz, $H4_A$), 1.39 (1H, dd, *J* = 16.3, 10.6 Hz, $H4_B$), 1.68 (1H, dd, *J* = 15.1, 8.8 Hz, $H3_A$), 1.74 (1H, dd, *J* = 15.1, 4.5 Hz, $H3_B$) 1.78 (1H, m, H5), 1.96 (1H, dd, *J* = 14.0, 10.6 Hz, $H1_A$), 2.16 (1H, m, H2), 2.25 (1H, dd, *J* = 14.6, 3.9 Hz, $H6_A$), 2.34 (1H, dd, *J* = 14.6, 7.3 Hz, $H6_B$), 2.61 (1H, dd, *J* =14.0, 7.3 Hz, $H1_B$), 3.88-3.98 (4H, m, $CO_2CH_2CH_3$ ×2); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.9 (2C), 18.1, 37.9, 38.5, 39.2, 39.4, 47.5, 57.9, 62.0, 62.2, 67.6, 115.3, 118.2, 171.4, 172.0; HRMS (ESI) calcd for $C_{16}H_{20}Cl_2N_2O_4Na$ $[M+Na]^+$ 397.0692, found 397.0687.



trans-isomer of **2a**

***trans*-Isomer of 2a:** yellow oil; IR (film) 2361, 1727, 1257, 1023 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 0.889 (3H, t, *J* = 7.3 Hz, CO_2CH_2), 0.892 (3H, t, *J* = 7.3 Hz, $CO_2CH_2CH_3$), 1.28 (1H, dd, *J* = 18.8, 7.6 Hz, $H4_A$), 1.29 (1H, m, H5), 1.38 (1H, dd, *J* = 18.8, 7.9 Hz, $H4_B$), 1.75 (1H, m, H2), 1.80 (1H, dd, *J* = 14.6, 9.0 Hz, $H3_A$), 1.88 (1H, dd, *J* = 14.6, 2.3 Hz, $H3_B$), 1.95 (1H, dd, *J* = 14.0, 8.0 Hz, $H6_A$), 2.00 (1H, dd, *J* = 13.5, 9.3 Hz, $H1_A$), 2.46 (1H, dd, *J* = 14.0, 7.3 Hz, $H6_B$), 2.80 (1H, dd, *J* = 13.5, 7.8 Hz $H1_B$), 3.91 (4H, m, $CO_2CH_2CH_3$ ×2); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.0 (2C), 20.5, 38.5, 40.1, 41.09, 41.15, 51.8, 58.7, 62.0, 62.1, 67.5, 115.4, 117.4, 171.1, 171.6; HRMS (ESI) calcd for $C_{16}H_{20}Cl_2N_2O_4Na$ $[M+Na]^+$ 397.0692, found 397.0704.

4.6. Synthesis of carbocycle 2b

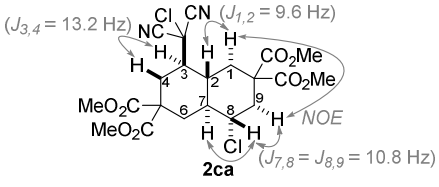


2b

According to the general procedure, carbocycle **2b** (25.1 mg, 67.0 μmol) was synthesized in 67% yield from enyne **1b** (23.8 mg, 0.100 mmol) by using CuCl (0.30 mg, 3.0 μmol), dppf (1.60 mg, 3.00 μmol) and $Cl_2C(CN)_2$ (50.0 μL, 0.500 mmol) in dioxane (10.0 mL). The residue was purified by flash chromatography on silica gel (1 g, hexane/EtOAc 10:1 to 3:1).

2b: yellow oil; IR (film) 2983, 2218, 1729, 1252, 859, 750 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.26 (3H, t, *J* = 7.3 Hz, $CO_2CH_2CH_3$), 1.27 (3H, t, *J* = 7.3 Hz, $CO_2CH_2CH_3$), 2.36 (1H, dd, *J* = 14.2, 7.7 Hz, $H1_A$), 2.67 (1H, dd, *J* = 14.6, 10.4 Hz, $H3_A$), 3.01 (1H, dd, *J* = 14.2, 8.4 Hz, $H1_B$), 3.12 (2H, m, H6), 3.26 (1H, dd, *J* = 14.6, 2.4 Hz, $H3_B$), 3.47 (1H, m, H2), 4.22 (4H, m, $CO_2CH_2CH_3$ ×2), 5.48 (1H, dd, *J* = 2.3, 2.3 Hz, H4); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.9 (2C), 39.3, 40.2, 42.0, 51.2, 58.9, 62.2, 62.4, 67.0, 94.8, 115.0, 115.3, 168.2, 169.9, 170.1; HRMS (ESI) calcd for $C_{16}H_{18}Cl_2N_2O_4Na$ $[M+Na]^+$ 395.0541, found 395.0528.

4.7. Synthesis of *trans*-decalin 2c

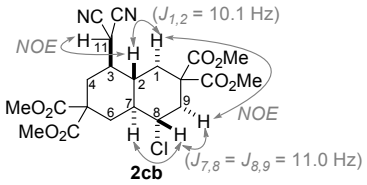


2ca

According to the general procedure, *trans*-decalin **2ca** (12.1 mg, 24.2 μmol) and **2cb** (4.00 mg, 8.53 μmol) were synthesized in 46%, and 16% yields, respectively, from *E*,*E*-diene **1c** (19.4 mg, 52.7 μmol), CuCl (0.16 mg, 1.6 μmol), dppf (1.20 mg, 1.58 μmol) and $Cl_2C(CN)_2$ (39.0 μL, 0.374 mmol) in dioxane (6.00 mL). The residue was purified by flash chromatography on silica gel (1 g, hexane/EtOAc 10:1 to 2:1).

2ca: colorless oil; IR (film) 2956, 2251, 1732, 1452, 1435, 1267, 1206 cm^{-1}; ^1H NMR (400 MHz, CD_3CN) δ 2.11 (1H, dd, *J* = 14.5, 5.3 Hz, $H9_A$), 2.24 (1H, dd, *J* =14.6, 9.6 Hz, $H1_A$), 2.35 (1H, dd, *J* =13.2, 13.2 Hz, $H4_A$), 2.47-2.57 (4H, m, $H1_B$, H2, H3, $H6_A$), 2.58-2.65 (2H, m, $H6_B$, H7), 2.76 (1H, dd, *J* =13.2, 6.4 Hz, $H4_B$), 2.94 (1H, dd, *J* = 14.5, 1.8 Hz, $H9_B$), 3.70 (3H, s,

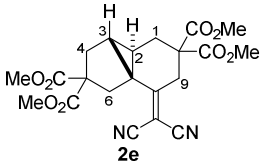
CO_2CH_3), 3.70 (3H, s, CO_2CH_3), 3.71 (3H, s, CO_2CH_3), 3.78 (3H, s, CO_2CH_3), 4.25 (1H, ddd, J = 10.8, 10.8, 2.3 Hz, H8); ^{13}C NMR (100 MHz, C_6D_6) δ 34.8, 39.0, 39.9, 44.1, 44.5, 46.9, 49.0, 49.4, 52.6, 52.7, 52.8, 52.9, 55.4, 58.4, 59.5, 112.2, 112.3, 170.0, 170.1, 171.6, 171.7; HRMS (ESI) calcd for $C_{21}H_{24}Cl_2N_2O_8Na$ $[M+Na]^+$ 525.0802, found 525.0787.



2cb

2cb: colorless oil; IR (film) 2956, 2360, 1732, 1436, 1250, 1205 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.95-2.01 (2H, m, H3, $H4_A$), 2.04 (1H, dd, J =14.0, 9.6 Hz, $H6_A$), 2.11 (1H, dd, J = 14.6, 10.1 Hz, $H1_A$), 2.19 (1H, dd, J =14.7, 11.0 Hz, $H9_A$), 2.34-2.44 (2H, m, H2, $H4_B$), 2.64-2.70 (2H, m, $H1_B$, H7), 2.85 (1H, ddd, J =14.0, 7.8, 1.4 Hz, $H6_B$), 3.05 (1H, ddd, J = 14.6, 1.8, 1.8 Hz, $H9_B$), 3.73 (3H, s, CO_2CH_3), 3.76 (3H, s, CO_2CH_3), 3.77 (3H, s, CO_2CH_3), 3.81 (3H, s, CO_2CH_3), 3.96 (1H, d, J = 3.2 Hz, H11), 4.07 (1H, ddd, J = 11.0, 11.0, 1.4 Hz, H8); ^{13}C NMR (100 MHz, $CDCl_3$) δ28.6, 36.3, 38.6, 39.5, 41.2, 43.4, 44.2, 48.6, 53.17, 53.19, 53.23, 53.5, 56.0, 58.1, 59.5, 110.2, 111.6, 170.18, 170.19, 170.9, 171.3; HRMS (ESI) calcd for $C_{21}H_{25}ClN_2O_8Na$ $[M+Na]^+$ 491.1192, found 491.1180.

4.8. Synthesis of tricycle 2e



2e

According to the general procedure, tricycle **2e** (22.0 mg, 51.1 μmol) was synthesized in 44% yield from enyne **1e** (42.2 mg, 0.115 mmol), CuCl (0.35 mg, 3.5 μmol), dppf (1.84 mg, 3.45 μmol) and $Cl_2C(CN)_2$ (59.0 μL, 0.575 mmol) in dioxane (12.0 mL). The residue was purified by flash chromatography on silica gel (1 g, hexane/EtOAc 10:1 to 2:1).

2e: colorless oil; IR (film) 2956, 2349, 1733, 1435, 1258, 1206 cm^{-1}; ^{1}H NMR (400 MHz, CD_3OD) δ 1.37 (1H, ddd, J = 7.7, 5.3, 5.3 Hz, H2), 1.63 (1H, dd, J = 14.3, 5.3 Hz, $H1_A$), 1.96 (1H, dd, J = 5.3, 5.3 Hz, H3), 2.62 (1H, d, J =14.2 Hz, $H4_A$), 2.68 (1H, d, J =14.2 Hz, $H6_A$), 2.74 (1H, ddd, J =14.3, 7.7, 2.3 Hz, $H1_B$), 2.77 (1H, dd, J =14.2, 5.2 Hz, $H4_B$), 2.85 (1H, d, J = 17.2 Hz, $H9_A$), 3.27 (1H, d, J = 14.2 Hz, $H6_B$), 3.44 (1H, dd, J = 2.0, 17.2 Hz, $H9_B$), 3.70 (3H, s, CO_2CH_3), 3.73 (3H, s, CO_2CH_3), 3.74 (3H, s, CO_2CH_3), 3.80 (3H, s, CO_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.4, 30.0, 34.5, 36.4, 37.6, 39.0, 41.5, 53.3, 53.38 (2C), 53.40, 54.6, 59.8, 87.1, 111.9, 112.1, 169.8, 170.0, 170.4, 172.5, 178.6; HRMS (ESI) calcd for $C_{21}H_{22}N_2O_8Na$ $[M+Na]^+$ 453.1268, found 453.1247.

4.9 Computational experiments

The conformational search of the 10-membered compounds **25c-e** was first conducted by molecular mechanics simulation using MacroModel.[18] The calculation was performed using a 1000-step of Monte Carlo-based torsional sampling (MCMM) and PRCG energy minimization with OPLS-2005 force field (gas phase). The obtained structures within 12 kcal/mol were transferred into Gaussian program [19] and optimized at PM6 semiempirical method (298 K, 1 atm, gas phase). The thus obtained structures within 2 kcal/mol were subjected to the geometry optimizations and frequency calculations at M06-2X/6-31G(d) level of theory (298 K, 1 atm, gas phase) to afford the most stable conformational isomer, which has no imaginary frequencies.

Acknowledgments

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Supplementary Material

NMR spectra of all new compounds and Cartesian coordinates for the optimized structures of **25c**, **25d** and **25e**.

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