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Substituted 1,3-cyclohexadiene synthesis by NHC–Nickel(0) catalyzed [2+2+2] cycloaddition of 1,*n*-Enyne

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ABSTRACT

This paper describes a catalytic and selective synthesis of substituted 1,3-cyclohexadiene fused with x*H*-pyran and furan. By using terminal enynes as substrates, NHC–Ni(0) as catalyst, and an ether as spacer between the two unsaturated hydrocarbon termini, the system competed with the terminal alkyne cyclotrimerization and yielded the desired [2+2+2] cycloaddition.

1. Introduction

The development of new catalytic processes for the synthesis of functionalized 1,3-dienes is important in organic synthesis. It is because 1,3-dienes are key building blocks for constructing a wide range of important organic frameworks for further applications, such as Diels–Alder reactions for higher substituted cyclic structures.[1] Transition metal catalyzed cycloadditions via metallacycle key intermediates have made remarkable progress in recent years,[2–6] and represents one of the most expedient ways of synthesizing cyclic 1,3-dienes. However, current technology is still awaiting further improvement because they are effective for only a subset of the possible range of precursors and partners. The most efficient cases are those either with structural features for conformational freedom reduction, with diynes as one of the reaction components, or with polarized π-systems to facilitate the key metallacycle intermediates formation. Both enynes and 1-alkynes are relatively less common substrates than diynes and internal alkynes,[7] especially for those with heteroatoms in the spacer between the two unsaturated hydrocarbon termini. This is possibly because 1) the enyne is electronically less activated, 2) the unfavorably high rotational freedom associated with those flexible heterosubstituted spacers, and 3) the highly competitive 1-alkyne cyclotrimerization to yield aromatic structures by a number of metal centers.[8,9]

Recently, we have developed a n^{γ}-*exo*-trig cycloisomerization of 1,*n*-heterosubstituted dienes (1,*n*-heterodienes)[10,11] by using an in situ generated [NHC–Ni(II)H(OTf)] catalyst (Fig. 1).[12,13] That

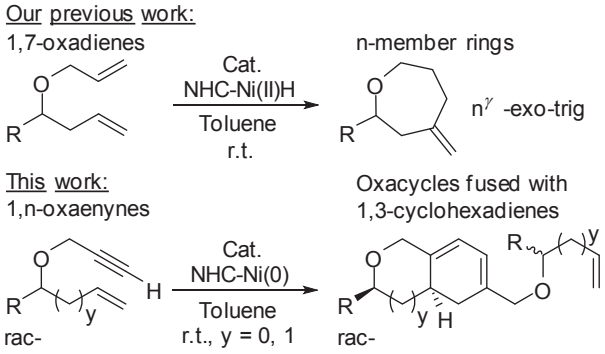

Fig. 1. NHC–Ni catalyzed 1,*n*-dienes cycloisomerization and enynes cycloaddition.

method synthesizes unsymmetrical *n*-member heterocycles out of the other possible heterocycles selectively by making use of the optimal γ-heteroatom chelation with the NHC–Ni(II) center. And that is good even for 1,*n*-heterodienes with very limited conformational constraints and/or with strong cycloisomerization

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competitions. The above prompted us to subject other substrates that may enjoy such a γ-heteroatom chelation and undergo cycloisomerization with the NHC–Ni(II)H catalyst, such as 1,*n*-heterosubstituted enynes (1,*n*-heteroenynes) for heterocyclic 1,3-dienes synthesis. In the meanwhile of that research, we found that simple 1,7-oxaenynes are rarely studied substrates in both cycloisomerization and cycloaddition. To tell apart the results from Ni(II)H and Ni(0) species, and in view of the fact that Ni(II)H can be reduced to Ni(0) under reaction conditions, we decided to step-back and first study the cycloaddition of 1,7-oxaenynes under Ni(0) condition with the relevant prior arts in the field in mind. Overall, we believe that should facilitate our development of cycloisomerization by Ni(II)H later on. To our delight, we discovered a [2+2+2] cycloaddition of 1,*n*-enynes **1** and **3** by using a NHC–Ni(0) catalyst (*n*=0, 1), yielded pyrans and furans with substituted 1,3-cyclohexadienes as products.

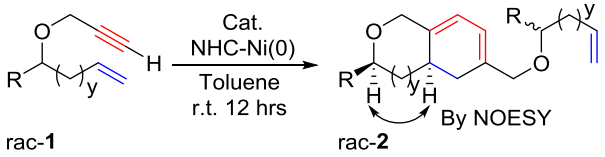
2. Results

The racemic 1,*n*-oxaenynes **1** with branched allyl or homoallyl ether structures, were prepared from the corresponding alcohol and propargyl chloride. The study were carried out by subjecting **1** to several in situ generated L-Ni(cod)$_2$ conditions at rt in toluene in order to obtain basic reactivity information (Table 1). By using only Ni(cod)$_2$ as catalyst, we found that the common cycloaddition side reactions, like 1-alkyne cyclotrimerization or isomerization of alkyne to allene, and cleavage of the propargylic ether were all observed as the major reaction outcomes (entries 1 and 8). These results showed that the structural features of the 1,*n*-oxaenyne **1a** and **1e** alone did not favor the enyne oxidative cyclization with Ni(0) and they just followed the typical side reactions of those carbon analogs. Next, several NHC–Ni(0) generated in situ were screened as catalyst at rt in toluene (entries 2–4). A significant difference in reactivity from the above was noted, and yielded a diastereomeric mixture of homo-[2+2+2] cycloaddition product 2**a**. The cycloaddition preferred a *syn*-relative configuration at the 1*H*-2-benzopyran core, which is similar to the NHC–Ni(0) catalyzed cycloaddition of internal enyne with aldehyde.[7a] Up to 83% yield of **2a** with less than 10% of alkyne cyclotrimerization were obtained by using IPr as ligand (entry 4). The system accepted substrates with R not only equals to phenyl, but also accepted those with simpler and more general alkyl chains, such as benzyl and nonyl (entries 5 and 6), yet not for **1** with R equals to H, which has a much higher degree of rotational freedom (entry 7).

Next, we also subjected 1,6-oxaenynes **1e** and **1f** to our reaction condition (entries 8–10). A [2+2+2] cycloaddition reactivity similar to the 1,7-oxaenynes was observed, yielded the corresponding hydro-isobenzofurans **2e** and **2f** regioselectively with reasonable yield. That bicyclic core was synthesized by using cationic Rh(I) catalyzed [2+2+2] cycloaddition in boiling ethanol in the literature,[14a,b] our method here provided an alternative at a relatively mild condition. It should be noted that Ni(cod)$_2$ was successfully used as stoichiometric catalyst in 1,6-enyne homo-[2+2+2] cycloaddition, the failure in entry 8 indicated that the importance of using NHC as ligand when a 1,6-oxaenyne was used as substrate for the preparation of oxacycles.[14c,d]

To study the effect of branching and the ether position relative to the unsaturated termini, racemic 1,*n*-oxaenynes **3** with branched propargyl or homopropargyl ethers were prepared and examined for the catalytic homo-[2+2+2] cycloaddition (Table 2). By simply applying the same optimized reaction condition as in Table 1, a diastereomeric mixture of product **4**, which has a structurally different bicyclic core as compared to **2**, was obtained in reasonable yield. Overall, the results in Tables 1 and 2 collectively showed that branched homopropargyl, propargyl, homoallyl, and allyl ethers are all compatible substrates of this system, and both aromatic and aliphatic substituents are tolerated. Unfortunately, the attempts that used oxaenynes with internal alkynes or alkenes, or nitrogen spacers as substrates were not successful.

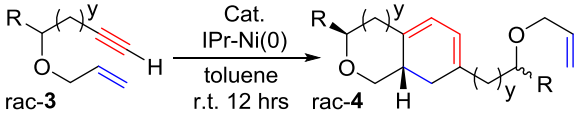
Table 1
Catalytic homo-[2+2+2] cycloaddition of 1,*n*-enynes **1** with branched allyl or homoallyl ethers[a]



Entry	NHC	R=	Y=	Enyne	Diene	Conver./Yield[b]
1	—	Ph	1	**1a**	—	100/0%
2	IMes	Ph	1	**1a**	**2a**	100/54%
3	SIPr	Ph	1	**1a**	**2a**	100/68%
4	IPr	Ph	1	**1a**	**2a**	100/83%
5	IPr	Bn	1	**1b**	**2b**	100/75%
6	IPr	Nonyl	1	**1c**	**2c**	100/81%
7	IPr	H	1	**1d**	—	100/0%
8	—	Ph	0	**1e**	—	100/0%
9	IPr	Ph	0	**1e**	**2e**	100/64%
10	IPr	Nonyl	0	**1f**	**2f**	100/72%

[a] See Experimental Section for details. Except otherwise indicated, all the reactions were carried out by adding the enyne to the following catalyst mixture: NHC and Ni(cod)$_2$ (10 mol % each, 0.05 mmol) with 2 mL toluene at rt. The relative stereochemistry on the substituted pyrans and furans **2** were assigned according to **2a** and **2e** by NOESY, and was compared with **5a** further (see later).
[b] Determined by both NMR and isolation as a diastereomeric mixture (~1:1).

Table 2
Catalytic homo-[2+2+2] cycloaddition of 1,*n*-oxaenynes **3** with branched propargyl or homopropargyl ethers[a]



Entry	R=	Y=	Enyne	Diene	Conver./Yield[b]
1	Butyl	0	**3a**	**4a**	100/72%
2	Ph	1	**3b**	**4b**	100/63%

[a] See Experimental Section for details. Except otherwise indicated, all the reactions were carried out by adding the enyne to the following catalyst mixture: IPr and Ni(cod)$_2$ (10 mol % each, 0.05 mmol) with 2 mL toluene at rt. The relative stereochemistry on substituted pyrans and furans **4** were determined by NOESY.
[b] Determined by both NMR and isolation, as a diastereomeric mixture (1:1).

We also tested the 1,7-oxaenyne for [2+2+2] co-cycloaddition (Fig. 2). Since the co-cycloaddition of benzaldehyde with the simple 1,7-enyne works efficiently (Eq. 1),[7a] we first examined the effect of ether spacer by using **1a**.[15,16]

Co-cycloaddition product **5a** and a diastereomeric mixture of **2a** were obtained in 3:1 ratio by using excess amount of benzaldehyde (Eq. 2). This indicated that the co-cycloaddition efficiency with benzaldehyde was lowered by the use of ether spacer (Eq. 1 vs 2). It also indicated that the co-cycloaddition with 1-alkyne might be favorable with the help of the ether spacer. Thus, we explored the co-cycloaddition of **1a** with additional 1-alkynes (1-hexyne or phenylacetylene, 1.5 equiv) under the standard reaction condition in Table 1. However, it did not undergo co-cycloaddition with **1a**, and yielded only **2a** at lower yield (35% and 45%) and cyclotrimerization products of the 1-alkyne as major reaction outcome.

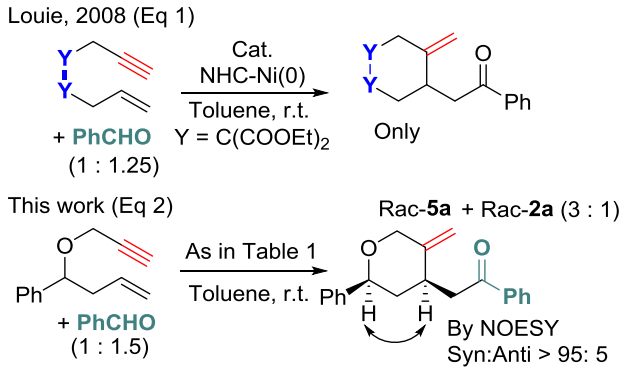
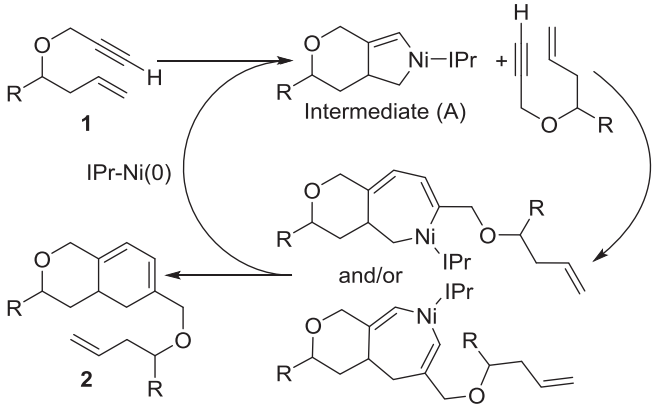


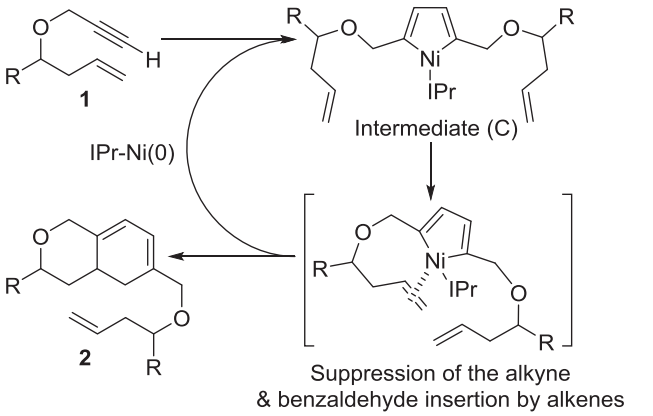
Fig. 2. Effects of the 1,7-enyne spacers in co-cycloaddition.[16]

We tentatively assumed that the mechanism of the 1,3-cyclohexadienes **2**, **4** and **6** formation could be explained simply according to the related [2+2+2] cycloadditions prior arts, which employed internal enynes as one of the partners (Scheme 1).[3b,7a]



Scheme 1. Proposed mechanism for the homo-[2+2+2] cycloaddition.

First, an intramolecular oxidative cyclization of the 1,*n*-enyne was directed by the NHC steric and electronic effects, yielded the nickelacyclopentene key intermediate (A) by using Ni(0) and the 1,*n*-oxaenyne. Next, the desired product was obtained and the catalyst was regenerated by a regioselective insertion of another enyne followed by a reductive elimination. It should be noted that the above proposed mechanism alone may not fully account for cases that employed 1,*n*-oxaenynes, in view of the following observations: i) the failure in using oxaenyne with internal alkyne as substrate in our system,[7a] ii) the changes in reactivity in Fig. 2 (i.e., the changes in rate of benzaldehyde and alkyne insertions to the common nickelacyclopentene intermediate), and iii) the attenuated cyclotrimerization observed.[8,9] As inspired by the facile 1-alkyne cyclotrimerization mechanism,[8] we hypothesize a minor alternation of the mechanism when an 1,*n*-oxaenyne is employed as substrate (Scheme 2). We believe that the formation of a symmetrical nickelacyclopentene intermediate (C) might be facilitated by the highly flexible ether spacer on 1,*n*-oxaenynes like **1** and **3**. Next, an intramolecular insertion of one of the two pending alkenes was allowed, which successfully suppressed the intermolecular insertions of the third alkyne to form the undesired cyclotrimerization products and yielded the desired products **2** and **4**. Yet, we are not able to observe intermediate (C) by spectroscopic technique or isolation, and thus a precise reaction mechanism awaits further study.



Scheme 2. A tentative mechanism for the [2+2+2] cycloaddition with structurally flexible 1,7-enynes.

Lastly, the stability of the 1,3-cyclohexadiene **2** deserves further attention. We found that the desired products **2a**–**c** reported in Table 1 were not stable at rt after isolation (Fig. 3). **2a**–**c** were converted completely to their isomeric structures **2′** after left those at rt for 10 days in neat form.[17] This process was monitored by TLC, ^{1}H and ^{13}C NMR according to the significant changes in Rf value and NMR spectra (the upfield shift of one of the OCH_2 signals, and the downfield shift of the diene CHs signals). After a complete conversion, the isolated structure **2′a** was further confirmed by HRMS and NMR as a 1:1 diastereomeric mixture, but the relative stereochemistry on the rings could not be determined by NOSEY. On the other hand, the product **4** was found stable after isolation and did not undergo a similar isomerization. Unfortunately, we cannot explain the differences in behavior among **2** and **4**.

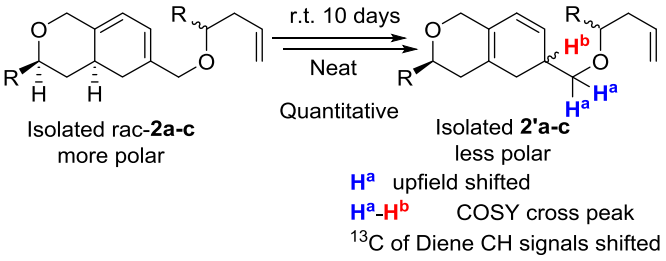


Fig. 3. Isomerization of **2** to **2′**.

3. Conclusion

We have discovered the first catalytic synthesis of substituted 1,3-cyclohexadienes fused with pyrans or furans by NHC–Ni(0) catalyzed homo-[2+2+2] cycloaddition of 1,*n*-oxaenynes. The experiments suggested that typical intramolecular oxidative cyclization intermediate formation may be not so favorable in case of using 1,*n*-oxaenynes as substrates. The choices of the spacers and the associated structural flexibility in the enynes may be the key factors and a possible strategy in controlling the cycloaddition outcomes and pathways. Hydro-isobenzofurans and 3 new types of 1*H*-2-benzopyrans like structures, **2**, **2′** and **4** were synthesized in reasonable yield by this new approach. The obtained information should be useful for our development in 1,*n*-hetero-substituted enynes cycloisomerization.

4. Experimental section

4.1. General

Unless otherwise indicated, all reactions were performed under a nitrogen atmosphere from, which oxygen and moisture were strictly excluded from the reagents and glassware. $Ni(cod)_2$ [Bis(-cyclooctadienyl)nickel(0)] was purchased from ACROS or IL, stored in a glovebox, and used without further purification. Toluene was distilled over sodium before use. IPr [1,3-Bis(2,6-diisopropyl phenyl)imidazol-2-ylidene], IMes [1,3-Bis(2,4,6-trimethylphenyl) imidazol-2-ylidene] and SIPr [1,3-Bis(2,6-di-*i*-propylphenyl)imidazolidin-2-ylidene] were purchased from TCI or Aldrich. 1,7-oxaenynes were dried with CaH_2 or $CaCl_2$ before use. Unless otherwise indicated, enynes were synthesized according to the procedures in the literature. Analytical thin layer chromatography (TLC) was performed with the use of EM Science silica gel 60 F_{254} plates. The developed chromatogram was analyzed by UV lamp (254 nm), ethanolic phosphomolybdic acid (PMA) or potassium permanganate ($KMnO_4$). Flash liquid chromatography was performed on a coarse fritted glass column packed with Grace Silica Gel (230–400 mesh, 0.040–0.063 mm). The cycloaddition products **2** were found not stable to store at rt. We recommend storing those below 0 °C. The preferred water bath temperature for rotavap is below 40 °C. ^1H and ^{13}C NMR spectra were recorded on Bruker spectrometers in $CDCl_3$ (400 MHz for ^1H and 100 MHz for ^{13}C). Chemical shifts in ^1H NMR spectra are reported in parts per million on the δ scale from an internal standard of residual chloroform (7.27 ppm). Chemical shifts of ^{13}C NMR spectra are reported in ppm from the central peak of $CDCl_3$ (77.16 ppm) on the δ scale. Cycloaddition precursors conversion and products ratio was determined by integration of areas of selected peaks in crude ^1H NMR with relaxation time $d1$=10 s and nitromethane/benzaldehyde as standard. High-resolution mass spectra (HRMS) were obtained on a Finnigan MAT 95XL.

4.2. General procedure for the NHC–Ni(0) catalyzed Homo-[2+2+2] cycloaddition of 1,*n*-Oxaenynes

In a glove box, $Ni(cod)_2$ and IPr (0.05 mmol, 10 mol % each) were added to an oven-dried test tube equipped with a stir bar. After being sealed with a septum and brought out of the glove box, the tube was connected to a N_2 line. The mixture was dissolved in 2 mL dried degassed toluene and stirred at rt for 1 h. The racemic 1,*n*-oxaenyne **1** or **3** (n=0, 1) was added to the above catalyst at rt. After stirring at rt for 12 h, the mixture was diluted with 4 mL of hexane, and was stirred in open air for 30 min. The mixture was then filtered through a short plug of silica gel and rinsed with 50 mL of 33% EA/hexane. The solvent was removed under a vacuum. Purification via silica gel column chromatography (1–5% EA/Hexane) yielded the racemic 1,3-cyclohexadiene product **2** or **4** as a mixture of diastereomers, respectively.

4.3. Procedure for the NHC–Ni(0) catalyzed [2+2+2] co-cycloaddition of 1,7-oxaenynes with benzaldehyde

The procedure is the same as the general procedure in 4.2, except 1.5 equiv of benzaldehyde was added before the addition of the oxaenyne.

4.4. Isomerization of 2 to 2′

The 1,3-cyclohexadiene product **2′** was obtained by simply left the isolated **2** in a rubber septum sealed round bottom flask at rt for 10 days in neat form. In all cases examined, **2′** is less polar than **2** and can be separated easily by column chromatography.

4.5. 1,*n*-Enynes preparation

The 1,*n*-enynes **1** and **3** were prepared from the corresponding alcohol in 70–85% yield according to the related literature.

1b: ^1H NMR (400 MHz, $CDCl_3$) δ: 7.38–7.14 (m, 5H), 5.95–5.77 (m, 1H), 5.13–5.05 (m, 2H), 4.13–4.08 (m, 2H), 3.78 (m, 1H), 2.86 (dd, J=14.0, 6.4 Hz, 1H), 2.76 (dd, J=14.0, 6.4 Hz, 1H), 2.37 (t, J=2.3 Hz, 1H), 2.34–2.20 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 138.6, 134.6, 129.6, 128.4, 126.3, 117.6, 80.2, 79.5, 74.1, 56.8, 40.2, 38.0. HRMS ESI (m/z): $[M+Na]^+$ calcd for $C_{14}H_{16}ONa$:223.1099; found 223.1094.

1c: ^1H NMR (400 MHz, $CDCl_3$) δ 5.83 (ddt, J=17.2, 10.0, 7.2 Hz, 1H), 5.08 (m, 2H), 4.18–4.17 (m, 2H), 3.53 (m, 1H), 2.39 (t, J=2.4 Hz, 1H), 2.31–2.26 (m, 2H), 1.54–1.20 (m, 16H), 0.88 (t, J=6.9 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 134.8, 117.1, 80.6, 78.3, 77.5, 77.2, 76.8, 73.8, 56.2, 38.1, 33.6, 32.0, 29.7, 29.7, 25.3, 22.8, 14.2. HRMS ESI (m/z): $[M+H]^+$ calcd for $C_{16}H_{28}O$:237.2174; found 237.2213.

1e: ^1H NMR (400 MHz, $CDCl_3$) δ 7.41–7.28 (m, 5H), 5.99–5.91 (m, 1H), 5.35–5.24 (m, 2H), 5.04–5.02 (d, J=8.0 Hz, 1H), 4.42–4.08 (m, 2H), 2.44–2.43 (t, J=4.0 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 140.0, 137.9, 128.6, 128.0, 127.2, 117.4, 81.3, 79.8, 74.5, 55.3. HRMS ESI (m/z): $[M+H]^+$ calcd for $C_{12}H_{13}O$: 173.0966; found 173.0962.

1f: ^1H NMR (400 MHz, $CDCl_3$) δ 5.67–5.58 (m, 1H), 5.25–5.21 (m, 2H), 4.10 (ddd, J=64.8, 15.6, 2.4 Hz, 2H), 3.85 (dd, J=14.4, 6.8 Hz, 1H), 2.38 (t, J=2.4 Hz, 1H),1.60–1.58 (m, 1H), 1.53–1.43 (m, 1H), 1.15–1.18 (m, 14H), 0.88 (t, J=9.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.2, 118.1, 80.4, 80.3, 73.8, 55.2, 35.3, 32.0, 29.7, 29.6, 29.4, 25.4, 22.8, 14.2. HRMS ESI (m/z): $[M+H]^+$calcd for $C_{15}H_{27}O$: 223.2062; found 223.2058.

3b: ^1H NMR (400 MHz, $CDCl_3$) δ 7.40–7.28 (m, 5H), 5.97–5.83 (m, 1H), 5.31–5.13 (m, 2H), 4.50 (m, 1H), 3.98 (ddt, J=12.8, 6.0, 1.2 Hz, 1H), 3.83 (ddt, J=12.8, 6.0, 1.2 Hz, 1H), 2.72 (ddd, J=16.8, 6.4, 2.8 Hz, 1H), 2.57 (ddd, J=16.8, 6.4, 2.8 Hz, 1H), 1.97 (t, J=2.7 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 134.7, 128.5, 128.2, 126.9, 117.3, 81.0, 79.4, 76.2, 70.1, 69.9, 28.2. HRMS ESI (m/z): $[M+H]^+$ calcd for $C_{26}H_{28}O_2$:187.1078; found 187.1117.

4.6. Spectroscopic data of 2 and 2′

2a: ^1H NMR (400 MHz, $CDCl_3$) δ: 7.38–7.27 (m, 10H), 5.81–5.50 (m, 3H), 5.11–4.90 (m, 3H), 4.52–4.18 (m, 4H), 3.97–3.68 (m, 1H), 2.87–1.67 (m, 6H), 1.67–1.54 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 142.4, 142.1, 142.0, 142.0, 138.1, 138.0, 136.8, 136.7, 135.2, 135.1, 135.1, 134.8, 134.7, 128.5, 128.5, 127.8, 127.7, 127.6, 127.0, 126.9, 125.9, 120.7, 120.7, 117.5, 117.4, 117.1, 117.0, 81.7, 81.7, 81.6, 81.6, 81.4, 81.3, 81.1, 81.0, 80.7, 79.7, 71.9, 71.6, 71.6, 71.3, 70.4, 70.3, 70.2, 70.2, 68.2, 68.0, 42.8, 42.7, 34.1, 32.5, 32.2. HRMS ESI (m/z): $[M+Na]^+$ calcd for $C_{26}H_{28}O_2Na$: 395.1987; found 395.1980.

2a′: ^1H NMR (400 MHz, $CDCl_3$) δ: 7.41–7.27 (m, 10H), 5.80–5.69 (m, 1H), 5.65–5.22 (m, 2H), 5.17–4.90 (m, 2H), 4.58 (td, J=10.4, 3.5 Hz, 1H), 4.38–4.16 (m, 3H), 3.32–3.15 (m, 2H), 2.76–2.62 (m, 1H), 2.59–2.17 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 142.5, 142.4, 142.4, 142.3, 135.2, 128.6, 128.5, 128.5, 127.7, 127.7, 126.8, 126.8, 126.6, 126.4, 126.4, 126.4, 126.1, 126.0, 125.6, 125.6, 123.4, 123.4, 116.9, 82.5, 82.3, 76.2, 76.2, 71.1, 71.0, 68.0, 68.0, 42.8, 37.3, 37.3, 34.7, 34.6, 30.6, 30.5. HRMS ESI (m/z): $[M+Na]^+$ calcd for $C_{26}H_{28}O_2Na$: 395.1987; found 395.1980.

2b: ^1H NMR (400 MHz, $CDCl_3$) δ 7.39–7.16 (m, 10H), 5.90–5.82 (m, 1H), 5.71–5.57 (m, 2H), 5.11–5.02 (m, 2H), 4.53–3.50 (m, 6H), 3.08–2.39 (m, 4H), 2.38–1.66 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 139.4, 139.3, 138.7, 138.6, 135.9, 135.8, 134.9, 134.9, 129.7, 129.5, 128.4, 128.4, 128.4, 128.3, 128.2, 126.4, 126.4, 126.2, 126.1, 121.0, 120.7, 117.5, 117.4, 117.2, 117.1, 79.5, 78.8, 78.3, 78.3, 72.5, 72.0, 71.3, 71.2, 42.7, 40.7, 40.6, 39.9, 39.7, 38.3, 38.0, 33.4, 33.3, 32.1, 32.0. HRMS ESI (m/z): $[M+Na]^+$ calcd for $C_{28}H_{32}O_2Na$: 423.2300; found 423.2293.

2b′: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.27–7.17 (m, 10H), 5.92–5.79 (m, 1H), 5.59 (dd, J=9.5, 2.9 Hz, 1H), 5.60–5.42 (m, 1H), 5.13–5.04 (m, 2H), 4.18–4.04 (m, 2H), 3.81–3.68 (m, 1H), 3.54–3.41 (m, 1H), 3.40–3.11 (m, 2H), 2.97 (ddd, J=13.7, 6.7, 2.6 Hz, 1H), 2.78–2.69 (m, 3H), 2.58–2.42 (m, 1H), 2.26 (dd, J=12.0, 6.1 Hz, 2H), 2.10–1.72 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 139.4, 139.2, 138.5, 135.1, 135.0, 129.7, 129.7, 129.5, 128.5, 128.3, 126.4, 126.2, 126.1, 125.4, 125.2, 123.5, 123.5, 117.4, 117.3, 81.0, 80.7, 75.0, 71.6, 71.4, 67.6, 42.4, 40.7, 40.6, 38.4, 38.3, 35.0, 35.0, 34.7, 34.6, 30.4, 30.1. HRMS ESI (m/z): $[M+Na]^+$ calcd for $C_{28}H_{32}O_2Na$: 423.2300; found 423.2293.

2c: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.92–5.55 (m, 3H), 5.17–5.01 (m, 2H), 4.88–3.82 (m, 4H), 3.58–3.28 (m, 2H), 2.66–1.85 (m, 6H), 1.52–1.37 (m, 5H), 1.29 (d, J=24.7 Hz, 28H), 0.88 (t, J=6.8 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 136.1, 135.4, 135.2, 124.3, 123.9, 120.6, 120.5, 117.7, 117.1, 116.8, 78.8, 78.4, 78.3, 77.6, 74.6, 74.4, 72.2, 72.2, 71.3, 70.9, 68.6, 68.3, 40.8, 40.7, 38.5, 38.4, 36.3, 34.0, 33.9, 33.7, 33.6, 32.7, 32.1, 32.1, 29.9, 29.9, 29.9, 29.8, 29.8, 29.8, 29.5, 25.8, 25.7, 25.5, 24.6, 23.7, 22.8, 14.2. HRMS ESI (m/z): $[M+H]^+$ calcd for $C_{32}H_{56}O_2$: 473.4314; found 473.4352.

2c′: ^{1}H NMR (500 MHz, $CDCl_3$) δ: 5.88–5.76 (m, 1H), 5.67–5.58 (m, 2H), 5.15–5.02 (m, 2H), 4.18–4.04 (m, 2H), 3.53–3.45 (m, 1H), 3.40–3.23 (m, 3H), 2.67–2.58 (m, 1H), 2.30–2.19 (m, 2H), 2.16–2.10 (m, 2H), 2.06–1.89 (m, 2H), 1.45 (m, 4H), 1.26 (m, 28H), 0.88 (t, J=6.9 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 135.4, 135.4, 126.4, 126.3, 126.2, 125.6, 123.6, 123.6, 116.8, 79.5, 79.5, 74.3, 71.3, 71.2, 67.6, 38.6, 38.6, 36.1, 35.6, 35.6, 34.9, 34.1, 34.1, 32.1, 30.7, 30.7, 29.9, 29.9, 29.8, 29.8, 29.7, 29.5, 29.5, 25.7, 25.6, 22.8, 14.2. HRMS ESI (m/z): $[M+H]^+$ calcd for $C_{32}H_{56}O_2$: 473.4314; found 473.4353.

2e: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37–7.26 (m, 10H), 5.98–5.79 (m, 3H), 5.28–5.15 (m, 2H), 4.81–4.74 (m, 2H), 4.58–4.51 (m, 2H), 4.00–3.93 (m, 2H), 2.77–2.72 (m, 1H), 2.25–2.12 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.9, 142.5, 142.4, 141.1, 140.5, 139.0, 138.8, 134.6, 133.3, 128.6, 128.6, 128.1, 127.8, 127.1, 127.0, 126.2, 122.4, 122.2, 120.9, 116.6, 116.5, 114.3, 113.5, 113.4, 87.9, 81.9, 81.8, 81.8, 71.4, 71.2, 70.4, 69.5, 48.0, 48.0, 47.7, 26.8, 25.1, 22.6. HRMS ESI (m/z): $[M+Na]^+$ calcd for $C_{24}H_{24}O_2Na$: 367.1776; found 367.1667.

2f: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.91–5.59 (m, 3H), 5.19–5.13 (m, 2H), 4.58–4.53 (m, 1H), 4.40–4.35 (m, 1H), 4.07–3.98 (m, 1H), 3.88–3.77 (m, 1H), 3.73–3.51 (m, 2H), 2.55–2.37 (m, 1H), 2.34–2.20 (m, 1H), 2.05–1.86 (m, 1H), 1.72–1.55 (m, 4H), 1.39–1.16 (m, 28H), 0.88 (t, J=6.4 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.4, 143.2, 139.5, 139.4, 139.3, 122.2, 120.5, 116.9, 114.1, 113.9, 113.0, 86.3, 86.3, 80.7, 80.6, 80.4, 71.5, 70.4, 70.3, 69.0, 45.3, 45.1, 44.8, 35.7, 35.6, 35.6, 35.5, 34.6, 32.0, 30.0, 29.7, 29.7, 29.5, 27.5, 26.3, 25.7, 25.7, 25.6, 25.6, 25.5, 22.8, 14.3. HRMS ESI (m/z): $[M+H]^+$calcd for $C_{30}H_{53}O2$: 445.4046; found 445.4041.

4.7. Spectroscopic data of 4

4a: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.97–5.67 (m, 3H), 5.30–5.13 (m, 2H), 4.55–4.41 (m, 1H), 4.31–4.19 (m, 1H), 4.08–3.87 (m, 1H), 3.83–3.71 (m, 2H), 3.51–3.39 (m, 1H), 2.99–2.80 (m, 1H), 2.40–2.21 (m, 1H), 1.96–1.72 (m, 1H), 1.54–1.10 (m, 12H), 0.94–0.86 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 146.7, 146.6, 136.6, 135.4, 135.3, 123.5, 123.2, 116.7, 113.3, 113.1, 82.7, 82.6, 80.0, 79.3, 74.1, 72.7, 69.2, 69.1, 40.5, 35.3, 34.6, 32.7, 28.2, 28.1, 25.1, 22.9, 22.8, 14.2, 14.2. HRMS ESI (m/z): $[M+H]^+$calcd for $C_{20}H_{33}O_2$: 305.2481; found 305.2475.

4b: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44–7.24 (m, 10H), 6.00–5.60 (m, 3H), 5.31–5.14 (m, 2H), 4.52–4.37 (m, 1H), 4.38–4.22 (m, 2H), 3.98–3.87 (m, 1H), 3.82–3.48 (m, 1H), 3.34–3.28 (m, 1H), 2.75–2.46 (m, 3H), 2.49–2.29 (m, 2H), 2.28–1.94 (m, 1H), 1.83–1.76 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 142.4, 142.4, 135.0, 134.2, 134.1, 133.1, 133.0, 128.5, 128.5, 127.7, 127.7, 126.9, 126.8, 125.9, 120.9, 120.7, 119.3, 119.2, 117.0, 117.0, 80.9, 80.5, 80.1, 80.1, 74.8, 74.8, 69.7, 69.6, 46.1, 46.1, 40.9, 40.8, 34.4, 30.0, 29.9. HRMS ESI (m/z): $[M+Na]^+$ calcd for $C_{26}H_{28}O_2Na$: 395.1987; found 395.1980.

4.8. Spectroscopic data of 5

5a: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99–7.22 (m, 10H), 5.00–4.76 (m, 2H), 4.65–4.62 (m, 1H), 4.41–4.22 (m, 2H), 3.42–2.93 (m, 3H), 2.14–2.10 (m, 1H), 1.54–1.39 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 198.8, 146.3, 142.1, 137.2, 133.4, 128.8, 128.5, 128.2, 127.7, 126.0, 108.1, 80.0, 73.9, 42.1, 40.8, 36.4. HRMS ESI (m/z): $[M+Na]^+$calcd for $C_{20}H_{20}O_2Na$: 315.1361; found 315.1354.

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Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2015.05.016.

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