Ti(Oi-Pr)$_4$-promoted photoenolization Diels–Alder reaction to construct polycyclic rings and its synthetic applications

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Stereoselective construction of polycyclic rings with all-carbon quaternary centers, and vicinal all-carbon quaternary stereocenters, remains a significant challenge in organic synthesis. These structures can be found in a wide range of polycyclic natural products and drug molecules. Here we report a Ti(Oi-Pr)$_4$-promoted photoenolization/Diels–Alder (PEDA) reaction to construct hydroanthracenol and related polycyclic rings bearing all-carbon quaternary centers. This photolysis proceeds under mild conditions and generates a variety of photo-cycloaddition products in good reaction efficiency and stereoselectivity (48 examples), and has been successfully used in the construction of core skeleton of oncocalyxones, tetracycline and pleurotin. It also provides a reliable method for the late-stage modification of natural products bearing enone groups, such as steroids. The total synthesis of oncocalyxone B was successfully achieved using this PEDA approach.

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Polycyclic rings containing anthracenols, anthraquinones and anthraquinones are ubiquitous in natural products and drug molecules. For example, the most well-known member of this family of natural products, doxorubicin (1) and tetracycline (2)\(^2\)\(^-\)\(^4\) (Fig. 1b), have been extensively studied as anticancer and antibiotic drugs. Interestingly, we also noticed a group of polyketides with all-carbon quaternary centers within the core anthracenols or anthraquinones, such as the newly isolated A-74528 (3)\(^5\)\(^-\)\(^6\) and JBIR-85 (4)\(^7\), as well as the antibiotics pleurotin (5)\(^8\)\(^-\)\(^13\) and oncocalyxone B (6)\(^14\)\(^-\)\(^15\). The additional quaternary carbons contribute to the diversity of these challenging chemical structures. Not surprisingly, these natural molecules show potential to be new anticancer or antibiotic agents. Notably, pleurotin (5) has attracted the attention of chemical and biological communities because of its potent activity against Gram-positive bacteria and its ability to inhibit the cellular redox system based on thioredoxin–thioredoxin reductase (half-maximal inhibitory concentration=170 nM). From the structural point of view, the basic skeletons (I–IV, Fig. 1a) of these natural polycycles feature linearly fused six-membered rings with various oxidation states and consecutive stereogenic centers, which represent the greatest challenge in their chemical synthesis.

To date, the Hauser annulation is one of the most commonly used methods for synthesizing anthraquinones from stabilized phthalides and Michael acceptors (Fig. 2a)\(^16\)\(^-\)\(^19\). This annulation involves tandem Michael addition/Dieckmann cyclization to generate para-anthracenols V, which can be easily oxidized to anthraquinones I. Alternatively, an ortho-toluate nucleophile can be used in this tandem process, in which case it is also known as Staunton–Weinreb annulation, and subsequent Michael addition/Dieckmann or Claisen condensation generates hydroanthracenol VI in a lower oxidation state (Fig. 2b)\(^20\)\(^-\)\(^22\).

Myers and co-workers\(^23\), \(^24\) have used this versatile methodology to prepare thousands of tetracycline derivatives. However, neither conventional Hauser annulation nor the Staunton–Weinreb variation can be used to construct hydroanthracenol IV, which has three consecutive stereogenic centers.

Photo-induced enolization of 2-alkyl benzophenones is an effective method to generate the active diene species hydroxy-oquinodimethane, which can be trapped by electron-deficient dienophiles to form the desired cycloaddition products 25. This methodology was first discovered by Yang and Rivas in 1961\(^26\), and it was further studied and applied in organic synthesis\(^20\)\(^-\)\(^23\), especially natural product total synthesis\(^24\)\(^-\)\(^28\)\(^-\)\(^29\). In 2004, Nicolaou and co-workers\(^30\)\(^-\)\(^33\) reported further studies of this reaction in both inter- and intra-molecular versions and its elegant applications in the total synthesis of hybocarpene, hammerans and their derivatives. In their work, mono-substituted and 1,1-disubstituted olefins were used as dienophiles in the intermolecular photoenolization/Diels–Alder (PEDA) reaction, generating the cycloaddition products in moderate stereocontrol. However, using sterically hindered 2,2-disubstituted olefin as a diene has been elusive\(^34\)\(^-\)\(^36\).

Since our research group is devoted to the synthesis of bioactive natural products, we decided to explore new approaches to prepare the core structure IV in a stereo-controlled way, which can serve as a common precursor for the synthesis of others (I–III) with higher oxidation states by simple oxidations. We also hope this method can be effectively utilized in the synthesis of 3–6 and their derivatives for biological and drug discovery studies. Here we report a method to synthesize IV, in which the target is prepared from 2-methylbenzaldehyde and Michael acceptors via titanium-promoted PEDA reaction. This method allows stereospecific formation of quaternary centers and convergent synthesis of related polycyclic natural products. As far as the intermolecular PEDA reactions are concerned, we realized

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**Fig. 1** Natural products containing anthracenols or anthraquinones. a The basic skeletons (I–IV) of hydroanthraquinones and hydroanthracenols contain linearly fused six-membered rings with various oxidation states and consecutive stereogenic centers. b Doxorubicin (1) and tetracycline (2) are anticancer and antibiotic drugs containing anthraquinone and anthracenol, respectively. A-74528 (3) and JBIR-85 (4), pleurotin (5) and oncocalyxone B (6) are structurally related polyketides bearing all-carbon quaternary centers within the core anthracenols or anthraquinones.
that the major challenges were: how to activate the poorly reactive 2,2-disubstituted dienophiles, and how to stabilize the short-lived photoenolized dienes. We speculated that this problem could be bypassed by adding Lewis or Bronsted acids to induce formation of a bichelated complex involving both diene and dienophile. This would temporarily turn an otherwise intermolecular PEDA into an intramolecular one, which would help to control the diastereoselectivity of the Diels–Alder reaction and stereospecifically form three consecutive stereogenic centers.

**Results**

**Optimization of reaction conditions.** We began our PEDA studies (Fig. 2c) using electron-rich 3,6-dimethoxy-2-methylbenzaldehyde (7) and electron-deficient 3-methylcyclohexone (8) as model substrates. When we tested the photoreaction conditions of Nicolau et al.,48 we found that ultraviolet (UV) irradiation (λ_{max}=366 nm) of a solution of 7 (1.0 equivalent (equiv.)) and 8 (6.0 equiv.) in degassed toluene for 2 h led to only trace amounts of hetero-cycloaddition product 11 and no formation of the desired cycloaddition product (Table 1, entry 1). This suggested that the active dihydro-o-quinodimethane species of 7 was generated and decomposed soon after photoenolization, before it could interact with the sterically hindered dienophile 8. We then tried to activate 8 by adding Bronsted or Lewis acids during photolysis. After extensive screening of 27 Bronsted and Lewis acids (entries 2–8, others see Supplementary Table 1), we were pleased to find that stoichiometric amounts of titanium(IV) isopropoxide Ti(Oi-Pr)4 (>2.0 equiv.) successfully promoted intermolecular [4 + 2] cycloaddition, giving the desired product 9 as a single diastereomer as well as its dehydration enone 10 in 56% combined yield (entry 8).52, 53 The relative configuration of 9 was confirmed by X-ray diffraction analysis. Alternatively, we were also able to substitute Ti(Oi-Pr)4 with metal triliate Lewis acid Yb(O2Tf)3, but the yield of 9 was very low (entry 7). We further optimized photolysis conditions by extensively screening solvents, additives and light sources in the presence of Ti(Oi-Pr)4 (for more details see Supplementary Tables 2–4). UV light at 300 nm gave similar yield as light at λ_{max}=366 nm, though the relative proportion of dehydrated product was greater (entry 9). Most solvents other than protic ones (e.g., ethanol) worked, including chlorobenzene, dichloromethane, acetonitrile and cyclohexane (entries 12–18). Notably, ether solvents such as diethyl ether and dioxane gave photolytic yields of 9 comparable to that obtained with toluene. Using anhydrous solvents slightly improved yield (entries 11, 17–19). Interestingly, we found that formation of dehydration product 10 was effectively suppressed when freshly recrystallized 7 was used in photolysis, affording 9 in 72% isolated yield. This may be because recrystallization removed small amounts of 3,6-dimethoxy-2-methylbenzoic acid, which could eliminate the β-hydroxy ketone of 9. We confirmed that this PEDA reaction requires both UV light and stoichiometric amounts of the Lewis acid Ti(Oi-Pr)4: no reaction occurred when the reaction mixture was stirred without irradiation in the presence of stoichiometric Ti(Oi-Pr)4 (entry 20). Obviously, activation of 2-methylbenzaldehyde by UV light initiates subsequent cycloaddition. It has been shown that this intermolecular cycloaddition depends strongly on the stoichiometry of Ti(Oi-Pr)4. We found that using a catalytic amount (0.2 equiv.) produced only trace amounts of 9, while using >2.0 equiv. provided optimal yield.

**Substrate scope.** We then investigated the scope of this PEDA reaction with respect to: the properties of diene (aromatic rings), the diversity of dienophiles and the potential application of the cycloaddition products. Using the β-substituted cyclohexenones as dienophiles, we planned to examine the generality of this photolysis for the construction of hydroanthracenol and related polycyclic rings (Table 2). We first tested easily available building blocks containing 3-methyl cyclohexenone moieties, such as piperitone (15) and isophorone (16). Under optimal conditions, photoreaction of 7 with 15 or 16 afforded the corresponding cycloaddition products 24 or 25 as single diastereomers in good yield. These results indicated that the substituents on the cyclohexenone ring did not affect the photolysis. Photolysis also tolerated substrates with hydroxyl and carbonyl functional groups or acid-sensitive protecting groups such as tert-butylidemethylsilyl ether (OTBS); in all cases, the desired product 26 with four consecutive stereogenic centers was obtained. Electron density on the diene ring did affect photolysis, with electron-donating substituents facilitating the photoreaction. Irradiation of monomethoxy-, trimethoxy- or fully substituted methylbenzaldehydes (12–14) with dienophiles (8, 15–17) stereospecifically generated the desired cycloaddition products (27–34) in synthetically useful yields. Notably, reaction efficiency increased with increasing electron density on the aromatic ring. We then explored reactions involving bicyclic dienophiles with two cis- or trans-fused six-membered rings (18 and 19). As we expected, irradiating 7 or 13 with 18 or 19 successfully furnished the desired tetracyclic products (35–38) bearing the basic skeleton of tetracycline and an additional quaternary center. The relative stereochemistry of tetracycline 36a was confirmed by X-ray diffraction analysis. We were pleased to find that photo-cycloaddition of the synthetically useful bicyclic building blocks Hajas–Parrish ketone (20) or Wieland–Miescher ketone (21), both of which contain an
enone group at the ring junction, smoothly gave rise to the desired tetracyclic rings (39–42) in moderate yields (24–61%) under optimal conditions. The chemical structure of compound 39 and its relative configuration were determined by X-ray diffraction analysis: this compound has the core structure and stereochemistry of pleurotin (5), potentially making it a useful intermediate en route to this challenging molecule and its derivatives. Moreover, two steroids, 4-cholesten-3-one (47) and norandrosterenedione (23), were selected as dienophiles in this PEDA reaction. We were surprised to find that the photoreaction worked well and formed the expected hexacyclic rings (43–46) in 59–76% yield. The structures of 44 and 45b were confirmed by X-ray diffraction analysis. These results highlight the ability of this PEDA approach to generate synthetically challenging steroid-containing architectures, which could potentially serve as scaffolds for drug discovery studies. It also shows the PEDA reaction to be an efficient method for late-stage modification of enone-containing natural products and drug molecules.

During our studies of reaction scope, we found that 2-methylbenzaldehyde substrates lacking a methoxy group ortho to the aldehyde showed no reactivity in this PEDA reaction. This identifies the ortho-methoxy group as crucial for the reaction, consistent with observations by Nicolau et al.49. The ortho-methoxy group was not required in the case of less sterically hindered dienophiles, as Nicolau et al.49 also found. We considered that the photoenolized hydroxy-α,\(\beta\)-quinodimethane and ortho-methoxy group may be chelated by Ti(O\((\text{Oi-Pr})_4\))\(_\text{a}\), forming a relatively stable complex. The ortho-methoxy may serve as a key neighboring group that helps to stabilize the short-lived photoenolized hydroxy-α,\(\beta\)-quinodimethane diene. Meanwhile, according to the findings of condition screening, using >2.0 equiv. Ti(O\((\text{Oi-Pr})_4\))\(_\text{a}\) provided optimal yields. These results suggest, taking model substrate as an example, that the reaction is driven by complexation of Ti(O\((\text{Oi-Pr})_4\))\(_\text{a}\) with both reactants 7 and 8. Next, we planned to further explore the generality and stereoselectivity of this PEDA reaction using 1,1-disubstituted olefins as dienophiles (Table 3). Both cyclic and acyclic olefins bearing a variety of electron-withdrawing groups, such as ketones (47–50), aldehydes (51–53) and esters (54 and 55), were investigated through the photo-cycloaddition with substituted 2-methylbenzaldehyde (7, 12–14). We found that a mixture of 7 and 2-methyl cyclohexene (47) or (48) underwent the Ti-promoted PEDA process and smoothly produced the desired products in good yields with endo/exo stereoselectivity ranging from 3:1 to 7:1. The photoreaction between 7 and 49 or 50 under the same conditions yielded 58 or 59, respectively, as single diastereomers. The structure and relative stereochemistry of 56a and 59 were confirmed by X-ray diffraction analysis. Meanwhile, as a control experiment, we also systematically investigated the reaction efficiency of 7 and 49, and the yield of the reaction increased obviously when the amount of Ti(O\((\text{Oi-Pr})_4\))\(_\text{a}\) increased from catalytic to stoichiometric (for more details see Supplementary Table 7). These results

| Entry | \(\lambda_{\text{max}}\) (nm) | Acid (3.0 equiv.) | Solvent\(\text{b}\) | Time (h) | Conversion (%)\(\text{c}\) | Yield (9 + 10, %)\(\text{c}\) | Yield (11, %)\(\text{c}\) | Ratio (9/10)\(\text{c}\) |
|-------|-----------------|-----------------|-----------------|--------|-----------------|-----------------|-----------------|-----------------|
| 1     | 366             | None            | Toluene         | 2.0    | 100             | ND              | Trace           | –               |
| 2     | 366             | TFA             | Toluene         | 3.5    | 82              | ND              | 5.4             | –               |
| 3     | 366             | PTSA-H\(_2\)O   | Toluene         | 3.5    | 87              | ND              | 1.3             | –               |
| 4     | 366             | TMSOTf          | Toluene         | 2.0    | 99              | ND              | ND              | –               |
| 5     | 366             | BF\(_3\)Et\(_2\)O | Toluene         | 2.0    | 60              | ND              | ND              | –               |
| 6     | 366             | Sc(OTf)\(_3\)   | Toluene         | 2.0    | 76              | ND              | ND              | –               |
| 7     | 366             | Yb(OTf)\(_3\)   | Toluene         | 2.0    | 98              | 16              | 0.8             | 2.2:1           |
| 8     | 366             | Ti(O\((\text{Oi-Pr})_4\)) | Toluene         | 0.5    | 100             | 56              | 1.6             | 14.3:1          |
| 9     | 300             | Ti(O\((\text{Oi-Pr})_4\)) | Toluene         | 0.75   | 96              | ND              | 55              | 3.2             | 4.8:1           |
| 10    | 254             | Ti(O\((\text{Oi-Pr})_4\)) | Toluene         | 1.5    | 98              | 19              | 1.5             | 3.4:1           |
| 11    | 366             | Ti(O\((\text{Oi-Pr})_4\)) | Toluene (dry)   | 0.5    | 100             | 60              | 2.9             | 20:1            |
| 12    | 366             | Ti(O\((\text{Oi-Pr})_4\)) | Chlorobenzene   | 0.5    | 100             | 61              | 3.4             | 12.5:1          |
| 13    | 366             | Ti(O\((\text{Oi-Pr})_4\)) | CH\(_2\)Cl\(_2\) | 1.5    | 100             | 36              | 5.6             | 12.1            |
| 14    | 366             | Ti(O\((\text{Oi-Pr})_4\)) | CH\(_2\)CN     | 2.0    | 94              | 22              | 8.0             | 6.2:1           |
| 15    | 366             | Ti(O\((\text{Oi-Pr})_4\)) | Et\(_2\)O     | 1.5    | 30              | ND              | Trace           | –               |
| 16    | 366             | Ti(O\((\text{Oi-Pr})_4\)) | Cyclohexane    | 0.5    | 100             | 67              | 4.8             | 4.8:1           |
| 17    | 366             | Ti(O\((\text{Oi-Pr})_4\)) | Et\(_2\)O (dry) | 0.5    | 100             | 61              | 4.0             | 16.7:1          |
| 18    | 366             | Ti(O\((\text{Oi-Pr})_4\)) | Dioxane (dry)  | 0.5    | 100             | 67              | 3.1             | 20:1            |
| 19\(\text{d}\) | 366 | Ti(O\((\text{Oi-Pr})_4\)) | Dioxane (dry)  | 0.5    | 100             | 72\(\text{e}\) | –               | 50:1            |
| 20    | None            | Ti(O\((\text{Oi-Pr})_4\)) | Dioxane (dry)  | 72.0   | 14              | ND              | ND              | –               |

\(\text{ND not detected}\)

\(=0.02\text{ mol/L}\)

\(=0.02\text{ mol/L}\)

=Recrystallized aldehyde (0.5 mmol) was used

\(=\text{Isolated yield}\)
Table 2 Scope of the PEDA reaction involving β-substituted cyclohexenones as dienophiles

| Compound | Yield | Stereoisomer Ratio |
|----------|-------|--------------------|
| 18 | 61% | 1:1.1:1.4 |
| 19 | 76% | 3.2:1 |
| 20 | 40% | (+)-Hajos-Parrish Ketone |
| 21 | 66% | Wieland-Miescher Ketone |
| 22 | 71% | 4-cholesten-3-one |
| 23 | 67% | norandrostenedione |
| 24 | 61% | 1:1:1.1 |
| 25 | 76% | 1:1:1.1 |
| 26 | 64% | X-ray |
| 27 | 40% | R1=H, R2=H, R3=H |
| 28 | 66% | R1=H, R2=H, R3=OMe |
| 29 | 67% | R1=Me, R2=H, R3=OMe |
| 30 | 67% | R=H |
| 31 | 72% | R=OMe |
| 32 | 63% | 1:1:1:1 |
| 33 | 84% | 1:1:1:1 |
| 34 | 82% | 1:1:1:1 |
| 35 | 49% | 1:1:1 |
| 36 | 52% | 1:1:1:1 |
| 37 | 48% | 1:1:1:1 |
| 38 | 62% | 2:8:1 |
| 39 | 32% | 1:1:1:1 |
| 40 | 24% | |
| 41 | 61% | 1:1:1:1 |
| 42 | 53% | 1:1:1:1 |
| 43 | 67% | 1:1:1:1 |
| 44 | | |

Method A: hv (λ<sub>max</sub>=366 nm), Ti(O<sub>i</sub>-Pr)<sub>4</sub> (3.0 equiv.), diene (0.3 mmol, 1.0 equiv.), dienophile (6.0 equiv.), conc. =0.02 mol/L, dioxane (anhydrous and degassed)

Method B: hv (λ<sub>max</sub>=366 nm), Ti(O<sub>i</sub>-Pr)<sub>4</sub> (1.2 equiv.), diene (0.3 mmol, 1.0 equiv.), dienophile (1.5 equiv.), conc. =0.02 mol/L, toluene (anhydrous and degassed)

Method C: hv (λ<sub>max</sub>=366 nm), Ti(O<sub>i</sub>-Pr)<sub>4</sub> (3.0 equiv.), dienophile (0.3 mmol, 1.0 equiv.), diene (2.0–4.0 equiv.), toluene (anhydrous and degassed)
indicate that the 1,1-disubstituted olefins used here, especially cyclic ones, also require the activation of Lewis acid Ti(Oi-Pr)4, which were in analogy to β-substituted cyclohexenones. Then, we turned our attention to aldehydes: all unsaturated aldehydes that we tested reacted well, giving endo/exo mixtures of the corresponding products 60–62. When the unsaturated ester 55 or lactone 54 were employed, the respective cycloaddition products 63 or 64 were acquired stereospecifically in good yield. Combining the dienophiles 49, 51 or 54 with different photoenolized dienes led to the expected products (65–73) with similar reaction efficiency and stereoselectivity. These results suggest that the structure of dienophiles as well as the properties of electron-withdrawing functional groups dramatically affect the stereoselectivity of photocycloaddition.

Additionally, we also tested 1,1,2,2-tetra-substituted olefins as dienophiles in this PEDA reaction in order to form products with contiguous all-carbon quaternary centers (Table 4). Construction of vicinal all-carbon quaternary stereocenters is extremely challenging in organic synthesis and natural product total synthesis54–56 because of the severe steric constraints. We first selected 2,3-dimethylcyclohexenone (74), which has one more methyl group than the model dienophile 8, in order to investigate its reactivity and stereoselectivity of the PEDA reaction. We were pleased to find that photolysis of 7 or 13 with 74 in the presence of Ti(Oi-Pr)4 under optimal conditions gave the desired products 78 and 79 as single diastereomers in respective yields of 38 and 56%. These products have the same relative stereochemistry as 9, based on single-crystal diffraction analysis of 78. We then
prepared three comparable substrates 75–77 with aldehyde, ketone or ester groups in order to study their influence on substrate reactivity in the PEDA process. We found that intermolecular photoreaction between 7 or 13 and dienophiles 75 or 76 underwent Ti-promoted PEDA reaction, producing the tricyclic products 80–83 in low to moderate yields. No desired cycloaddition products were observed under the same conditions when the photoreaction was performed between 7 or 13 and substrate 77, which contains an unsaturated ester group. These results indicate that the photoreaction of sterically hindered substrates depends strongly on the properties of electron-withdrawing groups on the dienophiles. Reaction efficiency increased with increasing electro negativity of the corresponding functional groups. Notably, this method generates products containing vicinal all-carbon quaternary stereocenters at the ring junctions (Table 4). Such molecules are not easily accessible through Hauser reactions, Staunton–Weinreb annulations or classical Diels–Alder reactions.

**Total synthesis of oncocalyxone B.** We believe that this PEDA reaction provides a solid basis for the preparation of hydroanthracenol and related polycyclic rings bearing all-carbon quaternary centers. To demonstrate the synthetic utility of this approach, we applied it to the total synthesis of oncocalyxone B, a cordiachrome family of unusual meroterpenoids isolated from the wood of *Auxemma oncocalyx* by Carvalho, Braz-Filho and co-workers in 1993 (Fig. 3a)14, 15. The bark of this plant is used as indigenous medicine to treat cuts and wounds. Biogenetically related molecules include oncocalyxone A (84)14, B (6)14, C (85)15, D (86)15 as well as glaziovianol (87)57, 58 (Fig. 3a). Oncocalyxone B (6) has a more challenging structure than the other members of this family with a hydroanthracenone skeleton and five consecutive stereogenic centers, including one all-carbon quaternary center at C-8a. An acetal moiety between two hydroxyl groups at C-8 and C-10 strains the ring skeleton.

Our synthesis started from the construction of the basic tricyclic ring via intermolecular PEDA reaction of 3,4,6-trimethoxy-2-methylbenzaldehyde (13) and electron-deficient 4-( tert-butyldimethylsilyloxy)-3-methylcyclohex-2-ene (17) under optimal conditions. UV irradiation (λmax=366 nm) of a solution of 13 and 17 in the presence of Ti(Oi-Pr)4 in degassed anhydrous toluene gave the desired product 88 in 76% yield (Fig. 3b). The relative stereochemistry of the four stereocenters was determined by X-ray diffraction analysis, which showed the orientation of the hydroxyl group at C-8 to be opposite to that in the naturally occurring molecule. To invert the C-8 stereocenter, the benzylic alcohol at C-10 was protected as the corresponding methoxymethyl ether, and the carbonyl group at C-5 was converted to a methylene group using Tebbe olefination, affording tricyclic compound 90 in 56% yield over two steps. Selective deprotection of the tert-butyldimethylsilyl ether followed by Dess–Martin oxidation and substrate-controlled reduction produced 91 bearing the desired hydroxyl group with good diastereoselectivity. During these efforts, we found 91 to be unstable in dichloromethane: it spontaneously transformed into 92, which has an oxygen bridge. The structure of 92 was unambiguously confirmed by X-ray diffraction analysis. We attributed the formation of 92 to the generation of a benzylic cation that underwent intramolecular trapping by the hydroxyl group at C-8. The methylene group at C-5 in 92 was functionalized into an α-aldehyde group, then we easily inverted the stereochemistry to the desired β-configuration (94) under basic conditions. Next, we screened various Lewis or Brønsted acids to install the bridged acetal group via a ring opening/acetalation process. We found that SnCl435, 60 smoothly catalyzed this tandem process and led to the formation of 95 in 85% yield. Subsequent CAN oxidation afforded oncocalyxone B (6) in 92% yield; 1H and 13C nuclear magnetic resonance (NMR) spectra and high-resolution mass spectrometry data for this synthetic compound were fully consistent with those of the natural product14, 15.

Table 4 Scope of the PEDA reaction involving 1,1,2,2-tetrasubstituted olefins as dienophiles

| R  | Product | Yield | Diastereoselectivity |
|----|---------|-------|----------------------|
| H  | 78      | 38%   | 11:1                 |
| OMe| 79      | 56%   | 11:1                 |
| OMe| 80      | 57%   | 17:1                 |
| OMe| 81      | 40%   | 17:1                 |
| OMe| 82      | 12%   |                      |
| MeO| 83      | 25%   |                      |
| ND |         |       |                      |

ND not detected

*Method: hv (λmax=366 nm), Ti(Oi-Pr)4 (3.0 equiv.), dienophile (0.4 mmol, 1.0 equiv.), diene (4.0 equiv.), dioxane (anhydrous and degassed)*
**Discussion**

In summary, a Ti(Oi-Pr)$_4$-promoted PEDA reaction was systematically studied. We found that stoichiometric amounts of the Lewis acid [Ti(Oi-Pr)$_4$] plays a key role in this photoysis. The advances of this developed PEDA reaction over previously reported methods rely on the high stereoselectivity and broad reaction scope. UV irradiation ($\lambda_{max} = 366$ nm) of mixtures of electron-rich 2-methylbenzaldehyde substrates bearing an ortho-methoxy group and various electron-deficient 1,1- or 2,2-disubstituted olefins in the presence of Ti(Oi-Pr)$_4$ smoothly generated hydroanthracenol and related polycyclic rings with good reaction efficiency and stereoselectivity. To the best of our knowledge, this is the first report that 2,2-substituted and 1,1,2,2-tetra-substituted olefins can serve as dienophiles in a PEDA reaction. This photoreaction is particularly useful for preparing hydroanthracenol and related structures with all-carbon quaternary centers, and even with all-carbon quaternary stereocenters, which has been demonstrated in the construction of core skeleton of tetracycline and pleurotin. This photo reaction also provides a reliable method for the late-stage modification of enone-bearing natural products such as steroids. This PEDA method was successfully used as a key reaction in the total synthesis of oncocalyxone B. We are currently studying the asymmetric PEDA reaction and its further applications to the total synthesis of complex natural products such as A-74528, JBIR-85 and pleurotin.

**Methods**

**General.** For $^1$H and $^{13}$C NMR spectra of the compounds in this article, see Supplementary Figs 1–82, and more experimental details and compound characterization data can be found in Supplementary Methods.

**General procedure for the titanium(IV)-promoted PEDA reaction.** To a solution of aromatic aldehyde (0.3 mmol, 1.0 equiv.) in anhydrous and degassed 1,4-dioxane (15 mL, 0.02 M) in quartz tube sealed with rubber plug was added dienophile (1.8 mmol, 6.0 equiv.) (if the dienophile was solid, it was added before the solvent) under N$_2$, then titanium(IV) isopropoxide (0.9 mmol, 3.0 equiv.) was added, and after homogeneous mixing, the solution was photolyzed at room temperature in a Rayonet chamber reactor (16 lamps) at $\lambda_{max} = 366$ nm for certain time. Then, the reaction mixture was poured into saturated sodium bicarbonate and stirred over 30 min, the above mixture was extracted three times with ethyl acetate and the combined organic phases were washed twice with brine and dried over anhydrous sodium sulfate. The dried solution was concentrated under vacuum. The residue was purified by column chromatography using silica gel chromatography to give the corresponding product. We generally used 6.0 equiv. dienophiles in the PEDA reactions because they are easily available and have small molecular weight. Such reactions were easy to handle. In reality, 1.5 equiv. dienophiles is sufficient for the reaction. For additional procedures see Supplementary Methods.

**Data availability.** The X-ray crystallographic coordinates for structures reported in this article have been deposited at the Cambridge Crystallographic Data Centre (CCDC). The data can be obtained free of charge from The Cambridge Crystallographic Data Centre via http://www.ccdc.cam.ac.uk/data_request/cif. The authors declare that the data supporting the findings of this study are available within the article. All other data are available from the authors upon reasonable request.
References

1. Arcamone, F. et al. New developments in antitumor anthracyclines. PharmacoL Ther. 76, 117–124 (1997).
2. Muckföld, H. Syntheses in the tetracycline series. Angew. Chem. Int. Ed. Engl. 1, 372–381 (1962).
3. Nicolau, K. C., Chen, J. S., Edmonds, D. J. & Estrada, A. A. Recent advances in the chemistry and biology of naturally occurring antibiotics. Angew. Chem. Int. Ed. 48, 660–719 (2009).
4. Wright, P. M., Seiple, I. B. & Myers, A. G. The evolving role of chemical
5. Fujita, Y. et al. Structural elucidation of A-74528, an inhibitor for 2
6. Hager, A., Mazunin, D., Mayer, P. & Trauner, D. Synthetic studies toward
7. Hart, D. J. & Huang, H.-C. Preparation of the CDE-ring system of pleurotin
8. Robbins, W. J., Kavanagh, F. & Hervey, A. Antibiotic substances from
9. Hart, D. J. & Huang, H.-C. Preparation of the CDE-ring system of pleurotin and geogrine via a stereoselective free radical cyclization. Tetrahedron Lett. 26, 3749–3752 (1985).
10. Hart, D. J. & Huang, H.-C. Total synthesis of (α)-pleurotin and (α)-dihydropleurotin acid. J. Am. Chem. Soc. 110, 1634–1635 (1988).
11. Hart, D. J., Huang, H.-C., Krishnamurthy, R. & Schwartz, T. Free-radical cyclizations: application to the total synthesis of dl-pleurotin and dl-dihydropleurotin acid. J. Am. Chem. Soc. 111, 7507–7519 (1989).
12. Kraus, G. A. & Chen, L. The development of a direct synthetic route to pleurotin. Synlett 2, 89–90 (1991).
13. Kraus, G. A. & Chen, L. Synthesis and evaluation of a pleurotin analog. Synth. Commun. 23, 2041–2049 (1993).
14. Pessoa, O. D. L., Lemos, T. L. G., Silveira, E. R. & Braz-Filho, R. Novel cordiacichlorines isolated from Auxemina oncolayx. Nat. Prod. Lett. 2, 145–150 (1993).
15. Pessoa, O. D. L., Lemos, T. L. G., Carvalho, M. G. & Braz-Filho, R. Cordiacichlorines from Auxemina Oncolayx. Phytochemistry 40, 1777–1786 (1995).
16. Hauser, F. M. & Rhee, R. P. New synthetic methods for the regioselective annelation of aromatic rings: 1-hydroxy-2,3-disubstituted naphthalenes and 1,4-dihydroxy-2,3-disubstituted naphthalenes. J. Org. Chem. 43, 178–180 (1978).
17. Mitchell, A. S. & Russell, R. A. Annulation reactions with stabilized phthalide anions. Tetrahedron 51, 5207–5236 (1995).
18. Rathwell, K. & Brimble, M. A. Use of stabilized phthalide anion annulation reactions in synthesis: an update. Synthesis 39, 643–662 (2007).
19. Mal, D. & Pahari, P. Recent advances in the Hauser annulation. Chem. Rev. 107, 1892–1918 (2007).
20. Evans, G. E., Leeper, F. J., Murphy, J. A. & Staunton, J. Triacetic acid lactone as a polycyclic skeleton: synthesis of toralactone and polycyclic-type anthracene derivatives. J. Chem. Soc. Chem. Commun. 12, 205–206 (1979).
21. Dodd, J. H. & Weinreb, S. M. Synthesis of the carbon framework of olivine. Tetrahedron Lett. 20, 3593–3596 (1979).
22. Donner, C. D. Tandem Michael-Dieckmann/Claisen reaction of o-benzylbenzophenone: a facile dimerization of naphthazarins to pentacyclic systems. J. Am. Chem. Soc. 118, 167–176 (1996).
23. Harwood, A. M. & Myers, A. G. Convergent enantioselective route to structurally diverse 6-deoxyxanthene antibiotics. Science 308, 395–398 (2005).
24. Wright, P. M. & Myers, A. G. Methodological advances permit the stereocontrolled construction of diverse fully synthetic tetracyclines containing an all-carbon quaternary center at position C5a. Tetrahedron 67, 9835–9869 (2011).
25. Sannes, P. G. Photoenolisation. Tetrahedron 32, 405–422 (1976).
26. Charlton, J. L. & S. Auddin, M. M. Orthoquinomedithiones. Tetrahedron 43, 2873–2889 (1987).
27. Segura, J. L. & Martín, N. o-Quinomethanides: efficient intermediates in organic synthesis. Chem. Rev. 99, 3199–3246 (1999).
28. Karkasa, M. D., Porco, J. A. Jr. & Stephenson, C. R. J. Photochemical approaches to complex chemotypes: applications in natural product synthesis. Chem. Rev. 116, 9683–9747 (2016).
55. Long, R., Huang, J., Gong, J.-X. & Yang, Z. Direct construction of vicinal all-carbon quaternary stereocenters in natural product synthesis. Nat. Prod. Rep. 32, 1584–1601 (2015).

56. Büschleb, M. et al. Synthetic strategies toward natural products contain contiguous stereogenic quaternary carbon atoms. Angew. Chem. Int. Ed. 55, 4156–4186 (2016).

57. Da Costa, G. M., De Lemos, T. L. G., Pessoa, O. D. L., Monte, F. J. Q. & Braz-Filho, R. Glaziovianol, a new terpenoid hydroquinone from Auxemma glazioviana. J. Nat. Prod. 62, 1044–1045 (1999).

58. Löbermann, F., Weisheit, L. & Trauner, D. Intramolecular vinyl quinone Diels–Alder reactions: asymmetric entry to the cordiachrome core and synthesis of (+)-isoglaziovianol. Org. Lett. 15, 4324–4326 (2013).

59. Nicolau, K. C. et al. Total synthesis of trioxacarcin DC-45-A2. Angew. Chem. Int. Ed. 54, 3074–3078 (2015).

60. Nicolau, K. C.; Cai, Q.; Sun, H.-B.; Qin, B. & Zhu, S.-G. Total synthesis of trioxacarcins DC-45-A1, A, D, C, and C7″-epi-C and full structural assignment of trioxacarcin C. J. Am. Chem. Soc. 138, 3118–3124 (2016).

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Author contributions
S.G. and B.Y. conceived the project and the synthetic route. S.G. directed the project. B.Y., K.L. and Y.S. conducted the work. S.G., B.Y. and K.L. analysed the experimental results. S.G. wrote the manuscript.

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