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Synthesis of Naturally Occurring Cyclohexene Rings Using Stereodirected Intramolecular Diels–Alder Reactions Through Asymmetric 1,3-Dioxane Tethering

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The utility of the readily available asymmetric 1,3-dioxane template in intramolecular Diels–Alder reactions is reported. The 1,3,9-decatrienoates substrates gave predominantly the *endo*-boat products, with minor amounts of the *exo*-boat isomer. Various substitutions (14 examples) were introduced and the results gave an indication of the scope and also a few limitations of the method. In particular, the approach was applicable to (*E*,*Z*)-diene substrates, for which good yields and selectivities were obtained. By applying suitable substrates, we describe the successful synthesis of valuable intermediates for the total synthesis of the diterpene harringtonolide (**1**) and the pyrrocidine polyketides (**2**), affording the appropriate stereochemistry of the natural product within the highly functionalized cyclohexene ring system. This is the first time that an asymmetric synthetic approach toward both compound series has been reported.

Introduction

In the course of our work on the total synthesis of natural products with chiral cyclohexane moieties, we studied the stereodirected intramolecular Diels–Alder reaction (IMDA).[1,2] This reaction has been used for decades but, depending on the natural target requirements, it is sometimes difficult to bring about because of unfavorable steric or electronic effects, low selectivity, or incompatibilities between fragile substrates and harsh reaction conditions. Nevertheless, many elegant achievements have been reported on the synthesis of complex natural products,[3] which have been extensively reviewed by others.[4] These works were possible only after careful analysis of substrate reactivity, with regard to the targeted structural features. Recently, we have been particularly interested in methodologies aimed at synthesizing two unrelated compounds: the diterpene harringtonolide (**1**)[5] and a number of polyketides in the pyrrocidine series (**2**)[6] and related compounds (hirsutellone B; **3**)[7] (Figure 1). We are now reporting our efforts on stereodirected IMDA reactions for the asymmetric synthesis of the cyclohexane ring system contained within these compounds.

To this end, template 1,3,9-decatrienoates precursors were designed on the basis of a chiral 1,3-dioxane tether. We assumed that stereocontrol of the IMDA reaction would be provided by some preferred conformation of the transition state, which would be guided by well-documented stereoelectronic effects.[2] It has been shown that positioning an internal carbonyl group on the dienophile strongly favors *endo*-boat transitions states in the case of 1,3,9-decatrienes, leading to *cis*-fused bicyclic systems, and that substituents on the decatrienoate tether can lead to important stereoselective preferences.[8] A chiral 1,3-dioxane tether was expected to make the decatrienoate system more rigid and to increase the possibility of efficient stereocontrol. Moreover, this particularly stable template would be useful in the case of less reactive substrates, especially *Z*-dienes, for which harsh thermal IMDA conditions are often required. Seeking the ideal 1,3-dioxane system, we found that common sugars could be well-suited starting materials; such compounds have a high density of stereocenters that are predisposed for transfer of asymmetry onto novel sp^3 centers and late functional group interconversions. In particular, D-glucose is a precursor of (1′*R*)-(–)-2,4-*O*-ethylidene-D-erythrose (**4**),[9] which is a C_4-building block with a potentially useful dual reactivity for selective functionalization (encompassing both a free nucleophilic hydroxyl group and an electrophilic aldehyde; Figure 2). This promising substrate was thus considered for our synthetic purpose.

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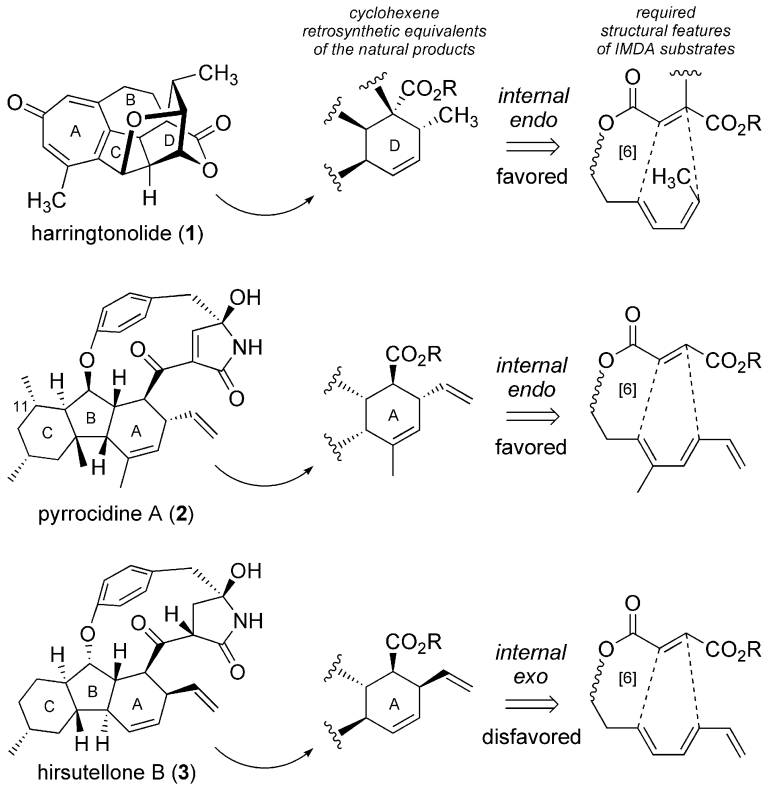


Figure 1. Natural products with an asymmetric cyclohexane ring that could arise from IMDA reaction and structural requirements for IMDA substrates.

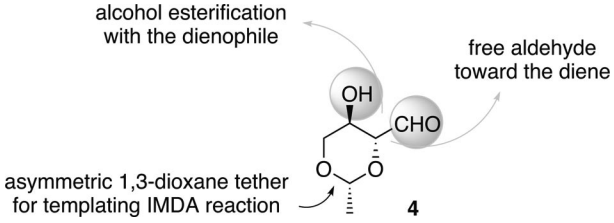


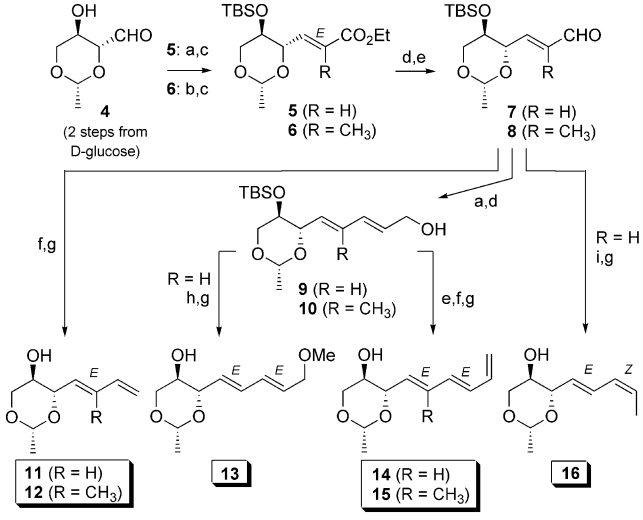
Figure 2. The dual functionality of (1′*R*)-(–)-2,4-*O*-ethylidene-D-erythrose (**4**) toward IMDA substrates.

Previously, the diastereoselectivity of the Diels–Alder reaction has only once been controlled with this type of chiral building block; in that case, the reaction was performed in an intermolecular manner in the total synthesis of forskolin.[10,11] To the best of our knowledge, the chiral 1,3-dioxane template was not used again until we reported a few years ago our first attempts to apply it to IMDA reactions.[12] Very recently, this template was again applied by others to intermolecular Diels–Alder reactions with diazadienophiles.[13] In all cases, the diastereomeric ratio resulted from important secondary orbital interactions depending on the dienophile, but the selectivity was also strongly influenced by steric interactions related to the substitution pattern. In our case, because the substrates contained an internal carbonyl within the 1,3,9-decatriene system, the *endo* mode was always preferred under thermal conditions, operating through boat transition states. The presence of a terminal ester on the dienophile (e.g., fumarate) improved the reaction outcome, but steric effects resulting from methyl substituents on both the diene and dienophile, proved to be much more important. We now report in detail the scope and limitations of this method.

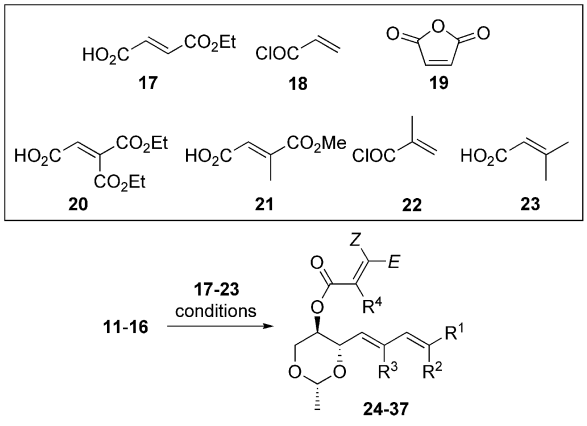
Results and Discussion

Synthesis of IMDA substrates: All 1,3,9-decatriene substrates were built from (1′*R*)-(–)-2,4-*O*-ethylidene-D-erythrose (**4**), which was synthesized in two steps from D-glucose (Scheme 1).[9] The diene part was assembled from the aldehyde function on the 1,3-dioxane ring. A Horner–Wadsworth–Emmons reaction was used first to install the *E* double bond within the α,β-unsaturated esters **5** and **6**, which were obtained after hydroxy *tert*-butyldimethylsilyl (TBS) ether protection. The α,β-unsaturated aldehydes **7** and **8** were formed by a reduction–oxidation sequence (diisobutylaluminum hydride (DIBAL-H) then MnO_2) from the esters. Wittig olefination allowed a collection of dienes **11**–**16** to be generated by divergent functionalization. Deprotection of the hydroxyl group and esterification with various dienophiles (fumarate, maleate, acrylate and substituted derivatives) finally gave the IMDA substrates (Scheme 2). Especially, the methylated (*E*,*Z*)-diene **16** and the (*E*,*E*)-triene **15** are remarkable intermediates for the synthesis of natural compounds **1** and **2**, respectively. The synthetic utility of the method was exemplified by a reaction sequence performed on a 30 g scale to generate (*E*,*Z*)-

diene **16** as a synthetic intermediate that can be used for the synthesis of diterpene **1**. Depending on the diastereomeric selectivity of the IMDA reaction, dienes **14** and **15** could also be interesting intermediates in the synthesis of pyrrocidines (**2**) with *cis* AB ring fusion, or hirsutellones (**3**) with *trans* AB ring fusion (Figure 1). The other dienes **11**–**13** will be used to assess the influence of substituents on the reactivity of the dienes.



Scheme 1. Divergent synthesis of the diene substrates. *Reagents and conditions:* (a) triethylphosphonoacetate, NaH, THF, 0 °C (74%); (b) triethylphosphonopropionate, BuLi, LiBr, MeCN, 0 °C (48%); (c) TBSCl, imidazole, DMAP, CH_2Cl_2, reflux (**5**: 86%; **6**: 90%); (d) DIBAL-H, CH_2Cl_2, –78 °C (**9**: 89%; **10**: 70%, two steps); (e) MnO_2, CH_2Cl_2, reflux (**7**: 92%; **8**: 78%, two steps); (f) $MePPh_3PBr$, NaHMDS, THF, –78 °C; (g) TBAF, THF, 0 °C (**11**: 70%; **12**: 67%; **13**: 85%; **16**: 84%, two steps; **14**: 90%; **15**: 58%, three steps); (h) NaH, THF, then MeI, 0 °C; (i) $EtPPh_3PBr$, NaHMDS, THF, –78 °C.

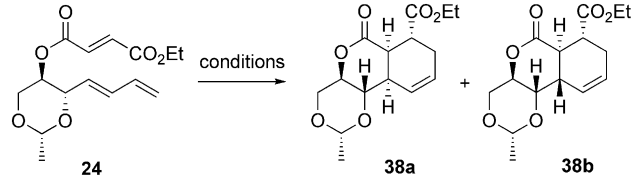


Scheme 2. The acylating dienophile reagents and the synthesis of the IMDA substrate series. *Reagents and conditions:* (a) for **17** and **23**: DCC, DMAP, CH_2Cl_2; (b) for **20** and **21**: MsCl, NEt_3, CH_2Cl_2; (c) for **18**, **19**, **22**: NEt_3/CH_2Cl_2. For compound correspondence, see Table 2.

Various acylating reagents (**17**–**23**) were used to introduce the dienophiles (Scheme 2). This allowed the electronic effect of internal versus terminal carboxylates, and the steric factors associated with the presence of methyl substituents to be compared. The tricarboxylate **20** and the mesaconate **21** were synthesized by applying the Wittig reaction between *tert*-butyl triphenylphosphoranylidene-acetate and either diethyl oxomalonate or methyl pyruvate,[14] respectively, before deprotection under acid (trifluoroacetic acid (TFA)) catalysis. All dienophiles were coupled to the dienes by esterification of the residual hydroxyl group of **11**–**16**, under variable conditions depending on the nature of the acylating reagent (Scheme 2).

Exploring the conditions of the Diels–Alder reactions: Starting from the readily accessible Diels–Alder substrate **24**, we found that heating of a 0.1 M solution of the compound to reflux in toluene at atmospheric pressure for 18 h, in the presence of sub-stoichiometric amounts of 2,6-di-*tert*-butyl-4-hydroxytoluene (BHT; 0.2 equiv.), afforded both stereoisomers **38a** and **38b** in 85 and 13% yield (87:13 ratio), respectively (Table 1, entry 1).[15] Heating of the same reaction mixture at 200 °C for only 1.5 h in a sealed tube gave **38a** and **38b** in 96% combined yield (86:14) (Table 1, entry 2). In *N*,*N*-dimethylformamide (DMF) (Table 1, entry 3) at reflux, the cycloadducts were obtained in 80% yield in a 83:17 ratio after only 1 h, whereas degradation was observed in dimethylsulfoxide (DMSO) at 200 °C (Table 1, entry 4), giving only 40% of **38a**. Cycloaddition also occurred when the reaction was catalyzed by a Lewis acid (Et_2AlCl) in dichloromethane at –30 °C (Table 1, entry 5). Under the latter conditions, however, degradation of the starting material led to a low yield of cycloadduct **38a** (33%), although complete selectivity seemed to occur in this case. Following these preliminary experiments, the use of toluene at elevated temperature, in the presence of a polymerization inhibitor (BHT), were established as the conditions of

Table 1. Optimization of the conditions for the IMDA reaction of substrate **24** toward the cycloadducts **38a** (*endo*-boat product) and **38b** (*exo*-boat product).



Entry	Conditions	*T* [°C]	*t* [h]	**a** [%]	**b** [%]	Ratio **a/b**
1	toluene, BHT (0.2 equiv.)	110	18	85	13	87:13
2	toluene, BHT (0.2 equiv.)[a]	200	1.5	83	13	86:14
3	DMF, BHT (0.2 equiv.)	153	1	66	14	83:17
4	DMSO, BHT (0.2 equiv.)[a]	200	1	40	0	100:0[b]
5	CH_2Cl_2, Et_2AlCl (1 equiv.)	–30→r.t.	15	33	0	100:0[b]

[a] Reaction was performed in a sealed tube. [b] Significant degradation was observed.

choice for this study. By controlling the tolerance of the reaction to steric and electronic factors, the scope and limitations of this method were then investigated.

Selectivity in the IMDA reaction of the 1,3-dioxane tethered substrates: With one exception (Table 2, entry 4), all the reactions that were worked up yielded only two of the four possible stereoisomers. When substrate **24** (Table 2, entry 1) was considered, four stereoisomers of the cycloadducts **38a**–**d** could indeed be found; these arose from combinations of *endo*/*exo* and boat/chair transition state conformers (see scheme in Table 2 and Figure 3).

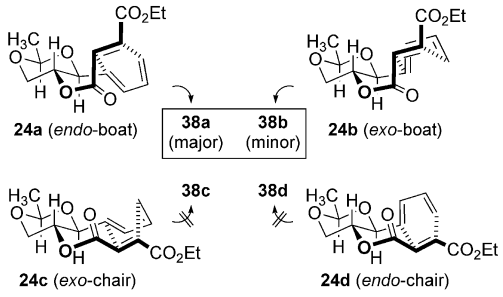
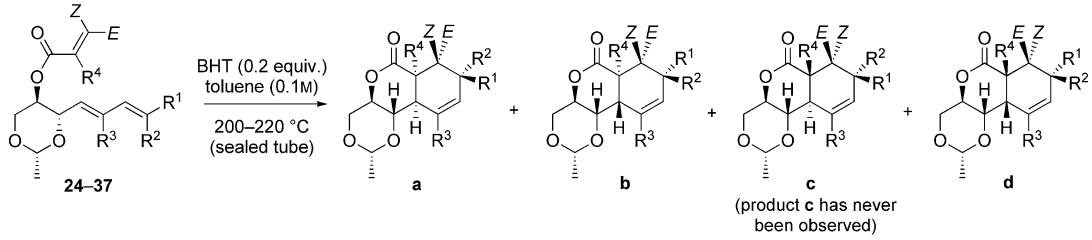


Figure 3. Four possible transition states to explain the selectivity of the IMDA reaction of 1,3-dioxane tethered substrates.

The stereoisomers **24c** and **24d**, arising from the chair transition states, were not observed, and only the products stemming from the boat transition states **24a** and **24b** were found (86:14 ratio). The dienophile thus always gave complete facial selectivity, whereas the diene part adopted two possible conformations relative to the dioxane ring. The major *endo*-boat transition state **24a**, with the CH-eclipsed diene, followed the *endo* rule with respect to the internal ester. Consequently, the *trans*,*cis*-fused 6-6-6 tricyclic system (**38a**) was the main product formed in this reaction. The *exo*-boat conformation **24b** afforded the minor *trans*,*trans*-isomer **38b**. This selectivity is consistent with previous reports,[8e,8f] which have often invoked *endo*-boat transition states to explain the observed selectivities. In our case, the observed results were also strongly influenced by constraints in the chiral dioxane tether, which tended to lower the entropy loss during the reaction.

Influence of substituents on the IMDA reaction: The *endo*/*exo* selectivity between boat transition states **a** and **b** ranged from nearly 50:50 to 96:4 (Table 2). We have shown with fumarate **24** (Table 2, entry 1) that the good stereoselectivity of the cycloaddition (86:14 ratio) followed the *endo*-rule with respect to the internal ester. However, secondary orbital interactions between the diene and the terminal ester in the *exo* transition state **24b** could be responsible for the formation of a significant amount of **38b**. Indeed, the use of an acrylate (**25**) instead of a fumarate led to an improved *endo*/*exo* ratio of 92:8 in favor of the isomer **39a** (Table 2, entry 2). However, maleate **26** gave a slightly lower 80:20 ratio of compound **40a** and **40b** (Table 2, entry

Table 2. Chemical diversity and reactivity of the Diels–Alder substrates.



Entry	IMDA substrate	Cycloadducts **a**–**d**	R^1	R^2	R^3	R^4	*E*	*Z*	*T* [°C]	*t* [h]	**a** [%]	**b** [%]	**d** [%]	Ratio **a**/**b**
1	**24**	**38**	H	H	H	H	CO_2Et	H	200	1.5	83	13	0	86:14
2	**25**	**39**	H	H	H	H	H	H	200	1	81	7	0	92:8
3	**26**	**40**	H	H	H	H	H	CO_2Me	200	2	74[a]	18[a]	0	80:20[a]
4	**27**	**41**	H	H	H	CH_3	H	H	220	144	17	–	11	–[b]
5	**28**	–	H	H	H	H	CH_3	CH_3	200	150	–	–	–	–[c]
6	**29**	**42**	H	H	H	H	CO_2Et	CO_2Et	200	4.5	45	49	0	48:52
7	**30**	**43**	H	H	H	H	CO_2Me	CH_3	200	48	70	22	0	76:24
8	**31**	**44**	H	H	CH_3	H	CO_2Et	H	200	2.5	94	4	0	96:4
9	**32**	**45**	CH_2OMe	H	H	H	CO_2Et	H	200	1	72	11	0	87:13
10	**33**	**46**	H	CH_3	H	H	H	H	220	72	44	24	0	65:35
11	**34**	**47**	H	CH_3	H	H	CO_2Et	H	220	110	66	21	0	76:24
12	**35**	–	H	CH_3	H	H	H	CO_2Me	220	72	–	–	–	–[c]
13	**36**	**48**	$CH=CH_2$	H	H	H	CO_2Et	H	200	1.3	38	–	–	–[c,d]
14	**37**	**49**	$CH=CH_2$	H	CH_3	H	CO_2Et	H	200	3	70	6	0	92:8

[a] Inseparable cycloadducts (94% global yield after purification). Specific yields and ratio were determined by NMR analysis. Both diastereoisomers were separated by chromatography after catalytic hydrogenation, and stereochemical assignments were then determined by 2D NMR spectroscopic analysis. [b] For this reaction, it was difficult to isolate all the products from the complex reaction mixture (with significant degradation being observed). The presence of other stereoisomers (i.e., **b** and **c**) cannot therefore be excluded. [c] Entries 5 and 13: significant degradation was observed; Entry 12: complete degradation was observed. [d] Comparable results were obtained at 110 °C with longer reaction times.

3), which we explained by unfavorable steric interactions between the maleate dienophile and the diene. Interestingly, when methacrylate **27** (Table 2, entry 4) was used, despite a long reaction time (144 h), it was possible to isolate 11% of the *endo*-chair cycloadduct **41d** beside the usual *endo*-boat derivative **41a**, which was obtained in 17% yield (Figure 4). The chair transition state **27d** would indeed be the conformation with minimized steric interactions. The alternative stereoisomers were not detected, although their formation could not be excluded because significant degradation was observed during the reaction. Moreover, this was the only experimental result of our work that contradicted the general boat stereoselectivity depicted in Figure 3. The results unambiguously revealed the strong steric effects associated with the use of a methacrylate-type dienophile with this kind of IMDA substrates.

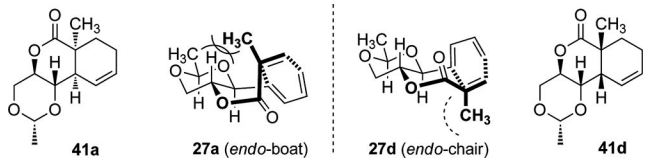


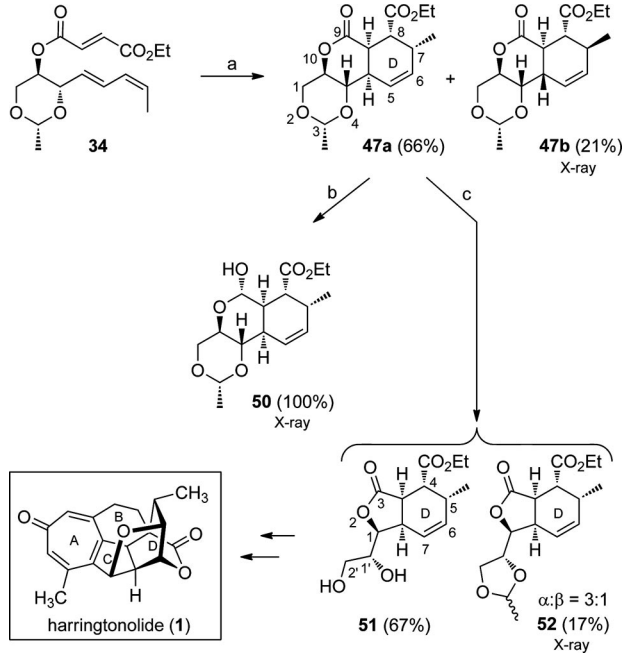
Figure 4. The outcome of the reaction with substrate **27** and steric interactions in the transition states explaining the unusual formation of cycloadduct **41d**.

The use of dimethylacrylate ester **28** (Table 2, entry 5) was even more discouraging because no cycloaddition product was detected in the reaction mixture and only degradation occurred after long reaction times at 200 °C (150 h). Nevertheless, tricarboxylate **29** (Table 2, entry 6) reacted quickly, giving 45 and 49% of the isolated cycloadducts **42a** and **42b**, respectively, after only 4.5 h at 200 °C. The selectivity in this reaction was, however, almost nonexistent, with a 48:52 ratio of both isomers being obtained; this contrasted with the results obtained in our previous experiments with fumarate **24** and maleate **26**. Finally, when mesaconate ester **30** (Table 2, entry 7) was used, we were pleased to achieve good selectivity and good yields in the IMDA reaction, giving 70 and 22% yield of stereoisomers **43a** and **43b**, respectively (ratio 76:24), and showing that the presence of β-substituents on the dienophile was not detrimental to the reaction.

We then turned our efforts towards the use of variously substituted dienes. The IMDA reactions in these cases were much more convincing, and allowed us to consider a number of promising applications. First, the presence of a methyl substituent as R^3 of the diene facing the fumarate on substrate **31** (Table 2, entry 8), compared to **24**, gave an excellent yield of the cycloadducts **44a** (94%) after 2.5 h at 200 °C, accompanied by the formation of only 4% of its stereoisomer **44b**, corresponding to a diastereofacial selectivity of 96:4. The presence of a terminal alkyl group (methoxymethyl) in the R^1 position of the diene (substrate **32**, Table 2, entry 9) also gave good yield and selectivity of cycloadducts **45a** and **45b**; a methyl group on the terminal R^2 position of the diene facing an acrylate dienophile (substrate **33**, Table 2, entry 10) led to 44 and 24% yield of cycloadducts **46a** and **46b** (ca. 2:1 selectivity), respectively. Although the latter reaction was performed at higher temperature (220 °C) and for a longer reaction time (72 h), the result was particularly interesting considering the harsh conditions used and the usually poor reactivity of (*E*,*Z*)-dienes in the Diels–Alder reaction.[16]

Synthetic utility of the 1,3-dioxane-templated Diels–Alder reactions: With such encouraging results and with the aim of synthesizing biologically important natural products (Figure 1), especially the diterpene harringtonolide (**1**) and polyketides such as pyrrocidine A (**2**), we applied our stereodirected IMDA reaction to substrates **34**–**37**.

Harringtonolide (**1**) is a diterpene isolated from the Chinese yew tree *Cephalotaxus harringtonia*.[5] It belongs to a small family of molecules all bearing a cage-shaped architecture and possesses a high biological value (phytotoxic, cytotoxic or antiviral properties). To build the highly functionalized cycle D of harringtonolide **1**, with the appropriate relative stereochemistry of every substituent (cycle D holds the entire stereochemistry of **1**), the use of fumarate ester **34** bearing an (*E*,*Z*)-diene was planned (Scheme 3). The *Z* geometry was important to introduce the methyl group on the α-side of the cycle. Preliminary experiments with fumarates (e.g., Table 2, entry 1) and with the (*E*,*Z*)-dienyl acrylate **33** (Table 2, entry 10) had indeed shown that the desired stereochemistry can be reached. Encouragingly, with substrate **34** (Table 2, entry 11), the reaction worked successfully, giving the expected *endo*-boat **47a** and *exo*-boat **47b** cycloadducts in 66 and 21% yields, respectively, thus significantly increasing the diastereofacial selectivity



Scheme 3. The 1,3-dioxane IMDA reaction applied to (*E*,*Z*)-dienyl fumarate **34**, as a key step in the synthesis of harringtonolide **1**. *Reagents and conditions:* (a) BHT (0.2 equiv.), toluene, 220 °C (sealed tube), 110 h; (b) L-Selectride, THF, –78 °C; (c) TFA/H_2O (1:1), 80 °C.

(ca. 3:1 ratio) compared with that obtained with substrate **33**. Although the reaction required 110 h at 220 °C to reach completion, the result was very good considering that this step was intrinsic to our retrosynthetic plan for the asymmetric total synthesis of this diterpene family of compounds. The reaction was performed on a multigram scale with high reproducibility. Moreover, we showed that this methodology would afford the correct absolute stereochemistry of the natural product.[17] Preliminary studies showed that the use of a maleate dienophile (**35**) instead of a fumarate (entry 12) only resulted in complete degradation.

An important achievement was the obtainment of crystals of compound **47b** and of the lactol derivative **50** from **47a**, that were suitable for X-ray crystallography (Figure 5).[18] The X-ray structures confirmed the NMR structure determinations and showed that the complete stereochemistry of the natural product **1** was correctly established. Furthermore, opening of the dioxane ring in acidic medium proved successful. No isomerization product (both carboxylic groups could be epimerized) was detected during this reaction, giving the reorganized diol **51** in 67% yield. At the same time, the recyclable dioxolane **52** was isolated, the α-isomer of which gave crystals that were suitable for X-ray analysis.

The pyrrocidines A (**2**) and B are polycyclic polyketides with antibiotic properties that are isolated from the fungus *Cylindrocarpon* sp.[6] These compounds are cytotoxic against leukemia HL-60 cells and share the same carbocyclic skeleton as hirsutellones (e.g., **3**),[7] but differ in the methylation pattern and the stereochemistry. According to the diastereofacial selectivity discussed above, we anticipated that using a fumarate and a vinylogous (*E*,*E*)-diene such as **36** or **37** would result in the correct relative stereochemistry of the cycloadduct. However, substrate **36** only afforded the *endo*-boat product **48a** in 38% yield after 1.3 h at 200 °C, with significant degradation of the starting material (Table 2, entry 13). Encouragingly, with the methylated analogue substrate **37**, it was pleasing to observe that high diastereofacial selectivity occurred (92:8) in favor of the expected cycloadduct **49a**, which was isolated in 70% yield after 3 h heating at 200 °C (Table 2, entry 14). Accordingly, **49a** bears the cycle A of pyrrocidines, and the high stereose-

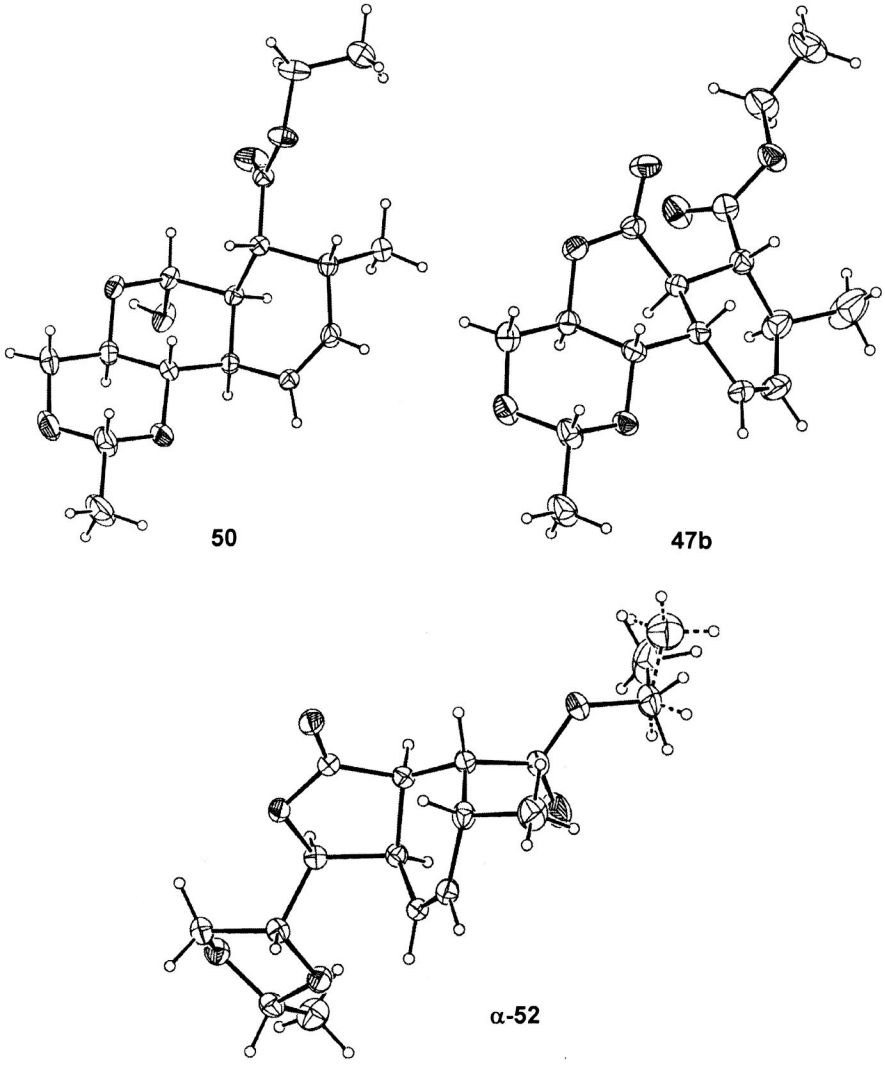
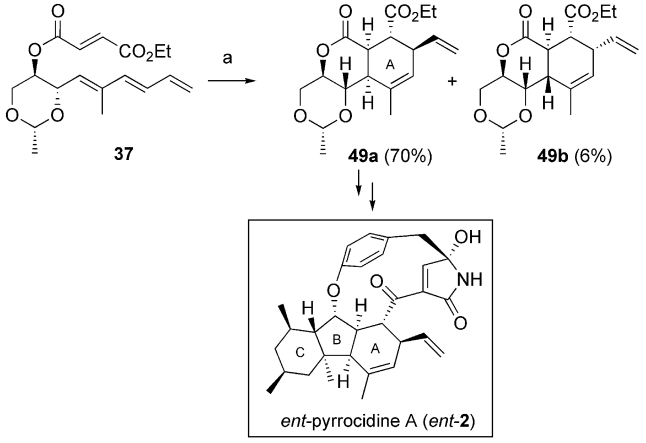


Figure 5. ORTEP drawings from X-ray crystallography of **47b**, **50** and **α-52**.

lectivity of the cycloaddition would be applicable to the total synthesis of *ent*-pyrrocidine *ent*-**2** (Scheme 4).[19] It is noteworthy that the *exo*-boat isomer (**49b**) holds a *trans*-ring fusion, with the relative stereochemistry of hirsutellones (**3**) and GKK1032 compounds.[20] The latter natural products have been synthetically approached using the Diels–Alder reaction of 1,3,8-nonatrienes, for which the IMDA reaction is known to proceed in the *exo* mode, to usually afford the *trans*-fused ring system.[21] To the best of our knowledge, this is the first time that a successful approach toward the *cis*-fused cyclohexene ring of pyrrocidines has been reported.



Scheme 4. The IMDA reaction of vinylogous (*E*,*E*)-dienyl fumarate **37**, as a key step in the total synthesis of *ent*-pyrrocidines A (**2**) and B. *Reagents and conditions:* (a) BHT (0.2 equiv.), toluene, 200 °C (sealed tube), 3 h.

Conclusions

During this work, we have demonstrated the utility and efficiency of the readily available asymmetric 1,3-dioxane template in intramolecular Diels–Alder reactions. All reactions yielded significant amounts of products resulting from *endo*-boat transition states. We studied the effect of various substitutions on the 1,3,9-decatrienoate systems, and showed that the only limiting situation was associated with the presence of alkyl and dialkyl substitutions on the α and β positions of the acrylate dienophile (Table 2, entries 4 and 5). Even an (*E*,*Z*)-diene gave good yields and selectivities (performed on a multigram scale from **34**), although harsher reaction conditions were required (Table 2, entries 10 and 11). This is a remarkable achievement because (*E*,*Z*)-dienes are often unsuitable substrates for Diels–Alder reactions and sometimes undergo undesirable side reactions such as [1,5]-sigmatropic rearrangements.[22] The results also showed that the 1,3-dioxane tether was resistant to harsh reaction conditions, such as high temperatures, over relatively long periods, but was easily removed in acidic medium. Finally, the methodology was applied to the synthesis of valuable intermediates that are suitable for the total synthesis of diterpene harringtonolide (**1**) from **34**, and of the pyrrocidine polyketides (e.g., **2**) from **37**. The key Diels–Alder reaction proved to be highly efficient in these projects. Moreover, it is the first time that an asymmetric synthetic approach toward both compound series has been reported.

Experimental Section

General Methods: Toluene was distilled in the presence of sodium/benzophenone just before use. All reactions were performed under argon. The products were isolated by flash silica gel column chromatography (Geduran silica gel Si 60; 40–63 μm). Thin layer chromatography (TLC) was conducted with Merck silica gel 60 F_{254} aluminum sheets (ref. 1.05554.0001). ^{1}H NMR spectra were recorded with a Bruker AC300 (300 MHz) or a Bruker Avance 400 spectrometer (400 MHz). ^{13}C NMR spectra were recorded with a Bruker AC300 spectrometer (75 MHz). High resolution mass spectra (HRMS) were measured with an Applied Biosystem QSTAR Pulsar-i spectrometer, using electrospray ionization. Infrared spectra were recorded with a Shimatzu 8400S FTIR spectrometer. Specific rotations were recorded with a Perkin–Elmer 341 polarimeter. Melting points were measured with a Büchi Melting Point B-545 apparatus. In the following sections, atom numbering follows that depicted for compounds **47a** and **51** in Scheme 3. More synthetic procedures concerning the Diels–Alder substrates (compounds **5**–**37**), copies of ^{1}H and ^{13}C NMR spectra, and crystallographic data are provided in the Supporting Information.

Ethyl (–)-(3*R*,4a*S*,4b*R*,8*R*,8a*R*,10a*R*)-3-Methyl-9-oxo-1,4a,4b,7,8,8a,9,10a-octahydro-2,4,10-trioxaphenanthrene-8-carboxylate (38a) and Ethyl (–)-(3*R*,4a*S*,4b*S*,8*R*,8a*R*,10a*R*)-3-Methyl-9-oxo-1,4a,4b,7,8,8a,9,10a-octahydro-2,4,10-trioxaphenanthrene-8-carboxylate (38b): A solution of triene **24** (52 mg, 0.169 mmol) in anhydrous toluene (1.7 mL) was heated at 200 °C in a sealed tube in the presence of BHT (7.5 mg, 0.034 mmol) for 1.5 h. The mixture was concentrated under reduced pressure and purified by flash chromatography (cyclohexane/ethyl acetate, 9:1) providing isomer **38a** (44 mg, 84%) as a colorless oil and isomer **38b** (7 mg, 13%) as a white solid.

Isomer 38a: $[\alpha]_D^{25}$ = –38.5 (*c* = 0.4, MeOH). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.78 (m, 2 H, 5-H and 6-H), 4.74 (q, *J* = 5.1 Hz, 1 H, 3-H), 4.34 (dd, *J* = 10.6, 5.2 Hz, 1 H, 1-H), 4.19 (m, 3 H, 10a-H and CH_2CH_3), 3.62 (m, 1 H, 8a-H), 3.57 (′t′, *J* = 10.3 Hz, 1 H, 1-H), 3.32 (m, 1 H, 8-H), 3.21 (′t′, *J* = 9.3 Hz, 1 H, 4a-H), 2.99 (m, 1 H, 4b-H), 2.56 (m, 1 H, 7-H), 2.47 (m, 1 H, 7-H), 1.38 (d, *J* = 5.1 Hz, 3 H, 3-Me), 1.26 (t, *J* = 7.1 Hz, 3 H, CH_2CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.9, 171.8, 126.2, 125.6, 99.9, 80.2, 68.0, 67.4, 61.1, 37.9, 37.2, 34.4, 22.8, 20.2, 14.1 ppm. IR (KBr): ṽ = 2992, 2926, 2866, 1758, 1725, 1196, 1043 cm^{-1}. HRMS (ESI$^+$): *m*/*z* [M + H$^+$] calcd. for $C_{15}H_{21}O_6$ 297.1338; found 297.1338.

Isomer 38b: M.p. 146 °C. $[\alpha]_D^{25}$ = –6.1 (*c* = 0.5, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.97 (m, 1 H, 5-H), 5.77 (m, 1 H, 6-H), 4.78 (q, *J* = 5.1 Hz, 1 H, 3-H), 4.33 (dd, *J* = 9.9, 4.6 Hz, 1 H, 1-H), 4.23 (m, 3 H, 10a-H and CH_2CH_3), 3.84 (dd, *J* = 10.0, 9.9 Hz, 1 H, 4a-H), 3.69 (′t′, *J* = 9.9 Hz, 1 H, 1-H), 3.10 (′t′, *J* = 11.4 Hz, 1 H, 8a-H), 2.85 (m, 2 H, 8-H and 4b-H), 2.57 (m, 1 H, 7-H), 2.28 (m, 1 H, 7-H), 1.39 (d, *J* = 5.1 Hz, 3 H, 3-Me), 1.29 (t, *J* = 7.2 Hz, 3 H, CH_2CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 174.3, 172.1, 126.1, 123.2, 100.6, 75.5, 69.8, 68.3, 60.9, 40.8, 40.5, 35.2, 29.3, 20.2, 14.1 ppm. IR (KBr): ṽ = 2991, 2941, 2874, 1768, 1736, 1189, 1038 cm^{-1}. HRMS (ESI$^+$): *m*/*z* [M + H$^+$] calcd. for $C_{15}H_{21}O_6$ 297.1338; found 297.1347.

(–)-(3*R*,4a*S*,4b*R*,8a*S*,10a*R*)-3-Methyl-9-oxo-1,4a,4b,7,8,8a,9,10a-octahydro-2,4,10-trioxaphenanthrene (39a) and (+)-(3*R*,4a*S*,4b*S*,8a*S*,10a*R*)-3-Methyl-9-oxo-1,4a,4b,7,8,8a,9,10a-octahydro-2,4,10-trioxaphenanthrene (39b): A solution of substrate **25** (46 mg, 0.205 mmol) in anhydrous toluene (2 mL) was heated in a sealed tube at 200 °C in the presence of BHT (8 mg, 0.041 mmol) for 1 h. The mixture was concentrated under reduced pressure and purified by flash chromatography (cyclohexane/ethyl acetate, 9:1), providing 41 mg of a 93:7 mixture of diastereoisomers **39a** and **39b**, respectively (NMR ratio). These isomers were separated by HPLC (SiO_2–C_{18} column, elution with water/acetonitrile/trifluoroacetic acid 70:30:0.005).

Isomer 39a: White solid; m.p. 96–97 °C; $[a]_D^{25}$ = –26.5 (*c* = 0.7, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 5.86 (m, 1 H, 6-H), 5.75 (m, 1 H, 5-H), 4.74 (q, *J* = 5.1 Hz, 1 H, 3-H), 4.29 (dd, *J* = 10.7, 5.2 Hz, 1 H, 1-H), 4.13 (m, 1 H, 10a-H), 3.56 (′t′, *J* = 10.2 Hz, 1 H, 1-H), 3.27 (′t′, *J* = 9.2 Hz, 1 H, 4a-H), 3.05 (m, 1 H, 8a-H), 2.80 (m, 1 H, 4b-H), 2.26 (m, 1 H, 7-H), 2.12 (m, 1 H, 8-H), 2.02 (m, 1 H, 7-H), 1.78 (m, 1 H, 8-H), 1.38 (d, *J* = 5.1 Hz, 3 H, 3-Me) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.5, 128.3, 125.5, 99.9, 79.8, 68.6, 68.1, 36.6, 36.3, 22.4, 21.6, 20.3 ppm. IR (KBr): $\tilde{\nu}$ = 3031, 2880, 1763, 1191, 1032 cm^{-1}. HRMS (ESI^+): *m*/*z* [M + H^+] calcd. for $C_{12}H_{17}O_4$ 225.1127; found 225.1126.

Isomer 39b: Colorless resin; $[a]_D^{25}$ = +44 (*c* = 0.2, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 5.95 (m, 1 H, 6-H), 5.78 (m, 1 H, 5-H), 4.79 (q, *J* = 5.1 Hz, 1 H, 3-H), 4.32 (dd, *J* = 7.5, 4.6 Hz, 1 H, 1-H), 4.18 (m, 1 H, 10a-H), 3.84 (′t′, *J* = 10.2 Hz, 1 H, 4a-H), 3.69 (′t′, *J* = 10.1 Hz, 1 H, 1-H), 2.83 (m, 1 H, 4b-H), 2.69 (m, 1 H, 8a-H), 2.25 (m, 2 H, 7-H and 8-H), 1.68 (m, 2 H, 7-H and 8-H), 1.40 (d, *J* = 5.1 Hz, 3 H, 3-Me) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.5, 128.1, 123.2, 100.6, 75.8, 70.0, 68.4, 39.2, 36.3, 25.0, 22.6, 20.2 ppm. IR (film on NaCl): $\tilde{\nu}$ = 2933, 2872, 1763, 1222, 1159, 1151, 1085, 1072, 1030 cm^{-1}. HRMS (ESI^+): *m*/*z* [M + H^+] calculated for $C_{12}H_{17}O_4$ 225.1127; found 225.1120.

Hydrogenation Product of Methyl (+)-(3*R*,4a*S*,4b*R*,8*S*,8a*R*,10a*R*)-3-Methyl-9-oxo-1,4a,4b,7,8,8a,9,10a-octahydro-2,4,10-trioxaphenanthrene-8-carboxylate (40a) and of Methyl (+)-(3*R*,4a*S*,4b*S*,8*S*,8a*R*,10a*R*)-3-Methyl-9-oxo-1,4a,4b,7,8,8a,9,10a-octahydro-2,4,10-trioxaphenanthrene-8-carboxylate (40b): A solution of substrate **26** (53 mg, 0.198 mmol) in anhydrous toluene (2 mL) was heated in a sealed tube at 200 °C in the presence of BHT (8 mg, 0.036 mmol) for 2 h. The mixture was concentrated and purified by flash chromatography (cyclohexane/ethyl acetate, 8:2), providing 50 mg of a 8:2 mixture (NMR ratio) of the two cycloadducts **40a** and **40b** (94% yield). For structural determination purposes, both compounds were separated after hydrogenation in the presence of Pd/C in methanol under a balloon of hydrogen. Purification was then performed by silica gel flash chromatography (cyclohexane/ethyl acetate, 9:1).

Hydrogenation Product of Isomer 40a: White solid; m.p. 92 °C; $[a]_D^{25}$ = +82 (*c* = 1, $CHCl_3$). ^1H NMR (300 MHz, CD_3OD): δ = 4.78 (q, *J* = 5.0 Hz, 1 H, 3-H), 4.35 (m, 1 H, 10a-H), 4.22 (dd, *J* = 10.1, 4.9 Hz, 1 H, 1-H), 3.76 (dd, *J* = 7.5, 4.9 Hz, 1 H, 8a-H), 3.65 (s, 3 H, CO_2Me), 3.62 (′t′, *J* = 10.1 Hz, 1 H, 1-H), 3.27 (dd, *J* = 9.7, 5.0 Hz, 1 H, 4a-H), 2.59 (′dt′, *J* = 12.5, 4.6 Hz, 1 H, 8-H), 2.18 (m, 1 H, 4b-H), 2.05 (m, 2 H, 5-H and 7-H), 1.79 (m, 1 H, 6-H), 1.57 (m, 1 H, 7-H), 1.30 (m, 4 H, 6-H and 3-Me), 0.97 (m, 1 H, 5-H) ppm. ^{13}C NMR (75 MHz, CD_3OD): δ = 175.3, 174.2, 101.3, 83.9, 70.4, 69.1, 52.3, 42.6, 40.6, 38.8, 32.6, 25.2, 24.4, 20.5 ppm. IR (KBr): $\tilde{\nu}$ = 2955, 2865, 1755, 1730, 1240, 1225, 1200, 1130, 1060, 920 cm^{-1}. HRMS (ESI^+): *m*/*z* [M + H^+] calcd. for $C_{14}H_{21}O_6$ 285.1338; found 285.1327.

Hydrogenation Product of Isomer 40b: White solid; m.p. 153 °C; $[a]_D^{25}$ = +59 (*c* = 1.1, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 4.74 (q, *J* = 5.1 Hz, 1 H, 3-H), 4.30 (dd, *J* = 10.3, 4.8 Hz, 1 H, 1-H), 4.10 (′dt′, *J* = 10.3, 4.8 Hz, 1 H, 10a-H), 3.80 (′t′, *J* = 10.3 Hz, 1 H, 4a-H), 3.71 (s, 3 H, CO_2Me), 3.64 (′t′, *J* = 10.3 Hz, 1 H, 1-H), 3.17 (m, 1 H, 8-H), 3.07 (m, 1 H, 4b-H), 2.48 (dd, *J* = 11.5, 3.6 Hz, 1 H, 8a-H), 2.17 (m, 1 H, 7-H), 2.03 (m, 1 H, 5-H), 1.78 (m, 1 H, 6-H), 1.62 (m, 1 H, 7-H), 1.39 (m, 1 H, 6-H), 1.35 (d, *J* = 5.1 Hz, 3 H, 3-Me), 1.29 (m, 1 H, 5-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.5, 172.2, 100.2, 75.7, 68.5, 68.3, 51.8, 44.4, 39.0, 32.4, 28.7, 26.1, 22.3, 20.3 ppm. IR (KBr): $\tilde{\nu}$ = 2996, 2955, 2875, 1767, 1735, 1233, 1193, 1152, 1132, 1072, 961 cm^{-1}. HRMS (ESI^+): *m*/*z* [M + H^+] calcd. for $C_{14}H_{21}O_6$ 285.1338; found 285.1339.

(–)-(3*R*,4a*S*,4b*R*,8a*S*,10a*R*)-3,8a-Dimethyl-9-oxo-1,4a,4b,7,8,8a,9,10a-octahydro-2,4,10-trioxaphenanthrene (41a) and (+)-(3*R*,4a*S*,4b*S*,8a*R*,10a*R*)-3,8a-Dimethyl-9-oxo-1,4a,4b,7,8,8a,9,10a-octahydro-2,4,10-trioxaphenanthrene (41d): A solution of substrate **27** (122 mg, 0.514 mmol) in anhydrous toluene (5 mL) was heated in a sealed tube at 220 °C in the presence of BHT (23 mg, 0.103 mmol) for 6 d. The mixture was concentrated under reduced pressure and purified by flash chromatography (cyclohexane/dichloromethane, 5:1) to provide isomer **41a** (21 mg, 17%) and isomer **41d** (13 mg, 11%) as colorless solids.

Isomer 41a: M.p. 105 °C; $[a]_D^{25}$ = –86 (*c* = 1.02, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 5.88 (m, 1 H, 6-H), 5.80 (m, 1 H, 5-H), 4.76 (q, *J* = 5.1 Hz, 1 H, 3-H), 4.22 (dd, *J* = 10.6, 5.0 Hz, 1 H, 1-H), 4.10 (m, 1 H, 10a-H), 3.55 (′t′, *J* = 10.4 Hz, 1 H, 1-H), 3.43 (dd, *J* = 9.3, 1.8 Hz, 1 H, 4a-H), 2.34 (m, 1 H, 4b-H), 2.14 (m, 2 H, 7-H), 1.83 (m, 2 H, 8-H), 1.38 (d, *J* = 5.1 Hz, 3 H, 3-Me), 1.36 (s, 3 H, 8a-Me) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 175.2, 127.5, 123.9, 99.9, 78.4, 71.5, 68.0, 43.8, 41.9, 30.7, 23.4, 21.3, 20.3 ppm. IR (film on NaCl): $\tilde{\nu}$ = 3036, 2993, 2928, 2874, 1735, 1466, 1411, 1377, 1273, 1234, 1199, 1145, 1091, 1041 cm^{-1}. HRMS (ESI^+): *m*/*z* [M + H^+] calcd. for $C_{13}H_{19}O_4$ 239.1277; found 239.1289.

Isomer 41d: M.p. 83 °C. $[a]_D^{25}$ = +24.1 (*c* = 0.78, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 6.04 (m, 1 H, 6-H), 5.82 (m, 1 H, 5-H), 4.82 (q, *J* = 5.0 Hz, 1 H, 3-H), 4.19 (dd, *J* = 9.9, 5.0 Hz, 1 H, 1-H), 4.11 (dd, *J* = 9.8, 5.0 Hz, 1 H, 10a-H), 3.95 (dd, *J* = 9.4, 4.3 Hz, 1 H, 4a-H), 3.58 (′t′, *J* = 9.6 Hz, 1 H, 1-H), 2.62 (m, 1 H, 4b-H), 2.32 (m, 1 H, 8-H), 2.04 (m, 2 H, 7-H), 1.45 (s, 4 H, 8-H and 8a-Me), 1.39 (d, *J* = 5.0 Hz, 3 H, 3-Me) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 175.1, 131.1, 123.8, 100.0, 74.5, 68.8, 68.1, 43.5, 42.8, 33.8, 29.0, 22.6, 20.3 ppm. IR (film on NaCl): $\tilde{\nu}$ = 2982, 2940, 2874, 1732, 1473, 1381, 1230, 1184, 1149, 1122, 1091, 1068, 1057, 1038 cm^{-1}. HRMS (ESI^+): *m*/*z* [M + Na^+] calcd. for $C_{13}H_{18}NaO_4$ 261.1097; found 261.1104.

Diethyl (–)-(3*R*,4a*S*,4b*R*,8a*R*,10a*R*)-3-Methyl-9-oxo-1,4a,4b,7,8,8a,9,10a-octahydro-2,4,10-trioxaphenanthrene-8,8-dicarboxylate (42a) and Diethyl (+)-(3*R*,4a*S*,4b*S*,8a*R*,10a*R*)-3-Methyl-9-oxo-1,4a,4b,7,8,8a,9,10a-octahydro-2,4,10-trioxaphenanthrene-8,8-dicarboxylate (42b): A solution of substrate **29** (50 mg, 0.136 mmol) in anhydrous toluene (1.3 mL) was heated in a sealed tube at 200 °C in the presence of BHT (6 mg, 0.027 mmol) for 4.5 h. The mixture was concentrated under reduced pressure and purified by flash chromatography (cyclohexane/ethyl acetate, 11:1) to provide isomer **42a** (23 mg, 45%) and isomer **42b** (24 mg, 49%) as colorless resins.

Isomer 42a: $[a]_D^{25}$ = –52 (*c* = 0.13, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 5.77 (m, 2 H, 5-H and 6-H), 4.72 (q, *J* = 5.0 Hz, 1 H, 3-H), 4.24 (m, 7 H, two CH_2CH_3, 1-H, 4a-H and 10a-H), 3.56 (′t′, *J* = 9.8 Hz, 1 H, 1-H), 3.20 (m, 2 H, 4b-H and 8a-H), 2.95 (dd, *J* = 18.1, 4.6 Hz, 1 H, 7-H), 2.75 (d, *J* = 18.1 Hz, 1 H, 7-H), 1.38 (d,

J = 5.1 Hz, 3 H, 3-Me), 1.23 (m, 6 H, two CH_2CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.7, 168.8, 126.3, 124.9, 99.9, 80.0, 67.9, 67.4, 62.3, 61.9, 54.6, 40.8, 36.6, 26.4, 20.2, 13.8 ppm. IR (film on NaCl): $\tilde{\nu}$ = 2928, 1739 (br), 1273, 1238, 1188, 1161, 1103, 1041 cm^{-1}. HRMS (ESI^+): m/z [M + H^+] calcd. for $C_{18}H_{25}O_8$ 369.1543; found 369.1555.

Isomer 42b: $[\alpha]_D^{25}$ = +79 (c = 0.06, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 5.91 (m, 1 H), 5.72 (m, 1 H), 4.76 (q, J = 5.0 Hz, 1 H), 4.25 (m, 6 H), 3.88 (′t′, J = 10.0 Hz, 1 H), 3.66 (′t′, J = 10.1 Hz, 1 H), 3.30 (d, J = 12.2 Hz, 1 H), 3.21 (m, 1 H), 3.09 (m, 1 H), 2.58 (m, 1 H), 1.36 (d, J = 5.1 Hz, 3 H), 1.27 (m, 6 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.2, 169.3, 168.7, 125.1, 123.8, 100.5, 75.3, 69.3, 68.2, 62.2, 61.7, 54.4, 44.1, 34.5, 32.7, 20.2, 13.9, 13.8 ppm. IR (film on NaCl): $\tilde{\nu}$ = 2982, 2924, 2854, 1774, 1724 (br), 1465, 1388, 1257, 1188, 1149, 1072, 906 cm^{-1}. HRMS (ESI^+): m/z [M + H^+] calcd. for $C_{18}H_{25}O_8$ 369.1543; found 369.1560.

Methyl (–)-(3*R*,4a*S*,4b*R*,8*R*,8a*R*,10a*R*)-3,8-Dimethyl-9-oxo-1,4a,4b,7,8,8a,9,10a-octahydro-2,4,10-trioxaphenanthrene-8-carboxylate (43a) and Methyl (+)-(3*R*,4a*S*,4b*S*,8*R*,8a*R*,10a*R*)-3,8-Dimethyl-9-oxo-1,4a,4b,7,8,8a,9,10a-octahydro-2,4,10-trioxaphenanthrene-8-carboxylate (43b): A solution of substrate **30** (60 mg, 0.20 mmol) in anhydrous toluene (2 mL) was heated in a sealed tube at 200 °C in the presence of BHT (9 mg, 0.04 mmol) for 48 h. The mixture was concentrated under reduced pressure and purified by flash chromatography (cyclohexane/ethyl acetate, 7:1) to provide isomer **43a** (42 mg, 70%) and isomer **43b** (13 mg, 22%) as colorless resins.

Isomer 43a: $[\alpha]_D^{25}$ = –25 (c = 0.25, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 5.78 (m, 1 H, 5-H), 5.64 (m, 1 H, 6-H), 4.71 (q, J = 5.1 Hz, 1 H, 3-H), 4.32 (dd, J = 10.4, 5.2 Hz, 1 H, 1-H), 4.21 (m, 1 H, 10a-H), 3.69 (s, 3 H, CO_2Me), 3.55 (′t′, J = 10.0 Hz, 1 H, 1-H), 3.46 (d, J = 9.0 Hz, 1 H, 8a-H), 3.19 (dd, J = 9.4, 8.1 Hz, 1 H, 4a-H), 2.97 (m, 1 H, 4b-H), 2.53 (m, 2 H, 7-H), 1.49 (s, 3 H, 8-Me), 1.37 (d, J = 5.1 Hz, 3 H, 3-Me) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 176.2, 170.4, 127.2, 125.5, 99.9, 80.3, 68.1, 67.3, 52.4, 44.3, 41.6, 37.2, 30.0, 23.2, 20.2 ppm. IR (film on NaCl): $\tilde{\nu}$ = 3032, 2997, 2939, 2874, 1759, 1724, 1458, 1377, 1203, 1161, 1138, 1111, 1072 cm^{-1}. HRMS (ESI^+): m/z [M + Na^+] calcd. for $C_{15}H_{20}NaO_6$ 319.1152; found 319.1152.

Isomer 43b: $[\alpha]_D^{25}$ = +33 (c = 0.35, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 5.93 (m, 1 H, 5-H), 5.73 (m, 1 H, 6-H), 4.76 (q, J = 5.0 Hz, 1 H, 3-H), 4.32 (dd, J = 10.1, 4.6 Hz, 1 H, 1-H), 4.23 (m, 1 H, 10a-H), 3.88 (′t′, J = 10.3 Hz, 1 H, 1-H), 3.71 (s, 3 H, CO_2Me), 3.68 (′t′, J = 9.9 Hz, 1 H, 4a-H), 3.31 (d, J = 12.7 Hz, 1 H, 8a-H), 2.91 (m, 1 H, 4b-H), 2.48 (m, 1 H, 7-H), 2.10 (m, 1 H, 7-H), 1.40 (d, J = 5.1 Hz, 3 H, 3-Me), 1.35 (s, 3 H, 8-Me) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 176.5, 171.5, 125.5, 122.6, 100.6, 76.0, 69.5, 68.3, 52.4, 43.6, 41.6, 37.8, 32.0, 20.2, 15.8 ppm. IR (film on NaCl): $\tilde{\nu}$ = 2958, 2924, 2854, 1763, 1732, 1465, 1261, 1149, 1072, 1018, 906 cm^{-1}. HRMS (ESI^+): m/z [M + Na^+] calcd. for $C_{15}H_{20}O_6$ 319.1152; found 319.1149.

Ethyl (–)-(3*R*,4a*S*,4b*S*,8*R*,8a*R*,10a*R*)-3,5-Dimethyl-9-oxo-1,4a,4b,7,8,8a,9,10a-octahydro-2,4,10-trioxaphenanthrene-8-carboxylate (44a): A solution of substrate **31** (330 mg, 1.06 mmol) in anhydrous toluene (10 mL) was heated in a sealed tube at 200 °C in the presence of BHT (47 mg, 0.21 mmol) for 2.5 h. The mixture was concentrated under reduced pressure and purified by flash chromatography (cyclohexane/ethyl acetate, 9:1→8:2) to provide isomer **44a** (310 mg, 94%) as a white solid and isomer **44b** (14 mg, contaminated by **44a**, 4% yield according to NMR analysis) as a colorless resin.

Isomer 44a: M.p. 59–60 °C; $[\alpha]_D^{25}$ = +34 (c = 1, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 5.43 (m, 1 H), 4.72 (q, J = 5.0 Hz, 1 H), 4.29 (dd, J = 10.5, 5.1 Hz, 1 H), 4.19 (m, 1 H), 4.12 (q, J = 7.1 Hz, 2 H), 3.60 (br. d, J = 10.0 Hz, 1 H), 3.54 (′t′, J = 10.0 Hz, 1 H), 3.24 (m, 2 H), 2.88 (′t′, J = 8.5 Hz, 1 H), 2.42 (m, 2 H), 1.66 (br. s, 3 H), 1.33 (d, J = 5.0 Hz, 3 H), 1.21 (t, J = 7.1 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.8, 171.7, 133.0, 121.1, 99.4, 79.4, 67.9, 67.1, 60.8, 37.9, 37.6, 26.8, 22.6, 21.1, 20.3, 14.0 ppm. IR (film on NaCl): $\tilde{\nu}$ = 2982, 2943, 2916, 2866, 1755, 1724, 1446, 1411, 1276, 1203, 1165, 1141, 1114, 1068, 887, 759 cm^{-1}. HRMS (ESI^+): m/z [M + H^+] calcd. for $C_{16}H_{23}O_6$ 311.1489; found 311.1483.

Ethyl (+)-(3*R*,4a*S*,4b*R*,7*S*,8*R*,8a*R*,10a*R*)-7-Methoxymethyl-3-methyl-9-oxo-1,4a,4b,7,8,8a,9,10a-octahydro-2,4,10-trioxaphenanthrene-8-carboxylate (45a) and Ethyl (–)-(3*R*,4a*S*,4b*S*,7*R*,8*R*,8a*R*,10a*R*)-7-Methoxymethyl-3-methyl-9-oxo-1,4a,4b,7,8,8a,9,10a-octahydro-2,4,10-trioxaphenanthrene-8-carboxylate (45b): A solution of substrate **32** (200 mg, 0.588 mmol) in anhydrous toluene (6 mL) was heated in a sealed tube at 200 °C in the presence of BHT (26 mg, 0.118 mmol) for 1 h. The mixture was concentrated under reduced pressure and purified by flash chromatography (cyclohexane/ethyl acetate, 9:1→4:1) to provide isomer **45a** (143 mg, 72%) and isomer **45b** (21 mg, 11%) as colorless resins.

Isomer 45a: $[\alpha]_D^{25}$ = +30 (c = 0.6, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 5.89 and 5.81 (2 × m, 2 H, 5-H and 6-H), 4.73 (q, J = 5.1 Hz, 1 H, 3-H), 4.27 (dd, J = 10.7, 5.2 Hz, 1 H, 1-H), 4.17 (m, 2 H, CH_2CH_3), 4.14 (m, 1 H, 10a-H), 3.58 (dd, J = 10.4, 5.4 Hz, 1 H, 8a-H), 3.54 (′t′, J = 10.2 Hz, 1 H, 1-H), 3.30 (m, 4 H, 7-CH_2OMe, 4a-H and 8-H), 3.28 (s, 3 H, OMe), 2.91 (m, 2 H, 4b-H and 7-H), 1.35 (d, J = 5.1 Hz, 3 H, 3-Me), 1.26 (t, J = 7.2 Hz, 3 H, CH_2CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.6, 171.0, 127.3, 126.6, 99.9, 78.8, 74.3, 69.6, 68.0, 61.3, 58.4, 42.2, 38.6, 37.2, 35.4, 20.3, 14.2 ppm. IR (film on NaCl): $\tilde{\nu}$ = 2984, 2933, 2875, 1760–1730 (br), 1142, 1078 cm^{-1}. HRMS (ESI^+): m/z [M + H^+] calcd. for $C_{17}H_{25}O_7$ 341.1600; found 341.1595.

Isomer 45b: $[\alpha]_D^{25}$ = –60 (c = 0.4, MeOH). ^1H NMR (400 MHz, $CDCl_3$): δ = 6.04 and 5.72 (2 × m, 2 H, 5-H and 6-H), 4.77 (q, J = 5.1 Hz, 1 H, 3-H), 4.22 (m, 4 H, 1-H, 10a-H and CH_2CH_3), 3.83 (′t′, J = 9.5 Hz, 1 H, 4a-H), 3.69 (′t′, J = 9.5 Hz, 1 H, 1-H), 3.31 (m, 2 H, 7-CH_2OMe), 3.24 (s, 3 H, OMe), 3.16 (′t′, J = 12.0 Hz, 1 H, 8a-H), 2.95 (dd, J = 11.1, 7.0 Hz, 1 H, 8-H), 2.87 (m, 1 H, 7-H), 2.79 (m, 1 H, 4b-H), 1.38 (d, J = 5.1 Hz, 3 H, 3-Me), 1.30 (t, J = 7.2 Hz, 3 H, CH_2CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.5, 172.4, 128.0, 124.4, 100.8, 75.6, 72.8, 70.0, 68.4, 60.8, 58.7, 42.5, 38.1, 37.6, 36.1, 20.3, 14.1 ppm. IR (film on NaCl): $\tilde{\nu}$ = 3039, 2985, 2935, 2875, 1767, 1732, 1676, 1469, 1450, 1413, 1392, 1381, 1367, 1340, 1265, 1203, 1180, 1161, 1151, 1112, 1074, 1035, 981 cm^{-1}. HRMS (ESI^+): m/z [M + Na^+] calcd. for $C_{17}H_{24}O_7Na$ 363.1420; found 363.1411.

(–)-(3*R*,4a*S*,4b*R*,7*R*,8a*R*,10a*R*)-3,7-Dimethyl-9-oxo-1,4a,4b,7,8,8a,9,10a-octahydro-2,4,10-trioxaphenanthrene (46a) and (–)-(3*R*,4a*S*,4b*S*,7*S*,8a*R*,10a*R*)-3,7-Dimethyl-9-oxo-1,4a,4b,7,8,8a,9,10a-octahydro-2,4,10-trioxaphenanthrene (46b): A solution of substrate **33** (31 mg, 0.13 mmol) in anhydrous toluene (1.3 mL) was heated in a sealed tube at 220 °C in the presence of BHT (7 mg, 0.033 mmol) for 3 d. The mixture was concentrated under reduced pressure and purified by flash chromatography (cyclohexane/diethyl ether, 8:1→6:1) to provide isomer **46a** (13 mg, 44%) and isomer **46b** (7 mg, 24%) as colorless resins.

Isomer 46a: $[\alpha]_D^{25}$ = –52 (c = 0.46, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 5.66 (m, 2 H, 5-H and 6-H), 4.70 (q, J = 4.4 Hz, 1 H, 3-H), 4.28 (dd, J = 10.7, 5.2 Hz, 1 H, 1-H), 4.11 (m, 1 H, 10a-H), 3.52 (′t′, J = 10.3 Hz, 1 H, 1-H), 3.18 (′t′, J = 9.1 Hz, 1 H, 4a-H), 3.06 (m, 1 H, 8a-H), 2.76 (m, 1 H, 4b-H), 2.38 (m, 1 H, 7-H), 2.25

(′dt′, *J* = 13.3, 4.2 Hz, 1 H, 8-H), 1.35 (d, *J* = 7.0 Hz, 3 H, 3-Me), 1.30 (m, 1 H, 8-H), 0.99 (d, *J* = 7.1 Hz, 3 H, 7-Me) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.8, 134.4, 124.9, 99.9, 80.4, 68.1, 67.9, 36.3, 35.8, 30.5, 25.9, 21.3, 20.3 ppm. HRMS (ESI$^+$): *m*/*z* [M + H$^+$] calcd. for $C_{13}H_{19}O_4$ 239.1283; found 239.1287.

Isomer 46b: $[\alpha]_D^{25}$ = –56 (*c* = 0.3, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.77 (m, 2 H, 5-H and 6-H), 4.75 (q, *J* = 5.0 Hz, 1 H, 3-H), 4.19 (dd, *J* = 10.5, 5.0 Hz, 1 H, 1-H), 4.09 (m, 1 H, 10a-H), 3.57 (′t′, *J* = 10.4 Hz, 1 H, 4a-H), 3.44 (dd, *J* = 11.1, 9.3 Hz, 1 H, 1-H), 3.02 (ddd, *J* = 12.9, 7.3, 3.7 Hz, 1 H, 4b-H), 2.66 (m, 1 H, 8a-H), 2.24 (m, 2 H, 7-H and 8-H), 1.38 (m, 4 H, 8-H and 3-Me), 1.04 (d, *J* = 7.0 Hz, 3 H, 7-Me) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.3, 135.6, 123.1, 100.1, 77.5, 72.1, 68.0, 40.1, 36.7, 34.1, 30.5, 21.1, 20.3 ppm. IR (film on NaCl): ṽ = 3055, 2985, 2928, 1743, 1419, 1203, 1141, 1111, 1080, 1045, 895 cm^{-1}. HRMS (ESI$^+$): *m*/*z* [M + H]$^+$ calcd. for $C_{13}H_{19}O_4$ 239.1283; found 239.1284.

Ethyl (–)-(3*R*,4a*S*,4b*R*,7*R*,8*R*,8a*R*,10a*R*)-3,7-Dimethyl-9-oxo-1,4a,4b,7,8,8a,9,10a-octahydro-2,4,10-trioxaphenanthrene-8-carboxylate (47a) and Ethyl (+)-(3*R*,4a*S*,4b*S*,7*S*,8*R*,8a*R*,10a*R*)-3,7-Dimethyl-9-oxo-1,4a,4b,7,8,8a,9,10a-octahydro-2,4,10-trioxaphenanthrene-8-carboxylate (47b): A solution of triene **34** (5.6 g, 18.1 mmol) in anhydrous toluene (180 mL) was heated in a sealed tube at 220 °C in the presence of BHT (800 mg, 1.81 mmol) for 5 d. The mixture was concentrated under reduced pressure and purified by flash chromatography (cyclohexane/ethyl acetate, 9:1→7:3) to provide isomer **47a** (3.26 g, 66%) as a colorless resin and isomer **47b** (1.03 g, 21%) as a crystallizable resin.

Isomer 47a: $[\alpha]_D^{25}$ = –94 (*c* = 1, CH_3OH). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.80 (m, 1 H, 5-H), 5.66 (m, 1 H, 6-H), 4.75 (q, *J* = 5.1 Hz, 1 H, 3-H), 4.33 (dd, *J* = 10.5, 5.3 Hz, 1 H, 1-H), 4.23 (m, 3 H, 10a-H and C*H*$_2$CH$_3$), 3.56 (dd, *J* = 10.5, 10.0 Hz, 1 H, 1-H), 3.43 (dd, *J* = 10.1, 3.4 Hz, 1 H, 8a-H), 3.29 (dd, *J* = 5.4, 3.4 Hz, 1 H, 8-H), 3.23 (′t′, *J* = 9.2 Hz, 1 H, 4a-H), 3.10 (m, 1 H, 4b-H), 2.73 (m, 1 H, 7-H), 1.39 (d, *J* = 5.1 Hz, 3 H, 3-Me), 1.27 (t, *J* = 7.2 Hz, 3 H, C*H*$_2$CH$_3$), 1.12 (d, *J* = 7.5 Hz, 3 H, 7-Me) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.3, 171.7, 131.3, 125.6, 99.9, 79.8, 68.0, 67.7, 60.7, 43.6, 38.3, 35.0, 28.1, 20.4, 17.9, 14.4 ppm. IR (KBr): ṽ = 2978, 2928, 2852, 1751, 1732, 1184, 1072 cm^{-1}. HRMS (ESI$^+$): *m*/*z* [M + Na$^+$] calcd. for $C_{16}H_{22}O_6Na$ 333.1314; found 333.1311.

Isomer 47b: M.p. 72–74 °C; $[\alpha]_D^{25}$ = +79.4 (*c* = 1.1, CH_3OH). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.90 (m, 1 H, 5-H), 5.60 (m, 1 H, 6-H), 4.78 (q, *J* = 5.1 Hz, 1 H, 3-H), 4.32 (dd, *J* = 10.3, 4.6 Hz, 1 H, 1-H), 4.23 (m, 4 H, 10a-H and C*H*$_2$CH$_3$), 3.83 (′t′, *J* = 10.2 Hz, 1 H, 4a-H), 3.68 (′t′, *J* = 10.0 Hz, 1 H, 1-H), 3.16 (′t′, *J* = 11.3 Hz, 1 H, 8a-H), 2.86 (m, 1 H, 4b-H), 2.53 (m, 1 H, 7-H), 2.42 (′t′, *J* = 10.6 Hz, 1 H, 8-H), 1.39 (d, *J* = 5.1 Hz, 3 H, 3-Me), 1.30 (t, *J* = 7.2 Hz, 3 H, CH$_2$C*H*$_3$), 1.15 (d, *J* = 6.9 Hz, 3 H, 7-Me) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 174.1, 172.0, 133.0, 121.9, 100.6, 77.4, 69.7, 68.3, 60.9, 48.6, 41.8, 35.7, 35.3, 20.2, 19.6, 14.2 ppm. IR (KBr): ṽ = 2993, 2870, 1759, 1728, 1180, 1149 cm^{-1}. HRMS (ESI$^+$): *m*/*z* [M + H$^+$] calcd. for $C_{16}H_{23}O_6$ 311.1489; found 311.1486.

Ethyl (+)-(3*R*,4a*S*,4b*R*,7*S*,8*R*,8a*R*,10a*R*)-3-Methyl-7-vinyl-9-oxo-1,4a,4b,7,8,8a,9,10a-octahydro-2,4,10-trioxaphenanthrene-8-carboxylate (48a): A solution of substrate **36** (200 mg, 0.62 mmol) in anhyrous toluene (6 mL) was heated in a sealed tube at 200 °C in the presence of BHT (28 mg, 0.12 mmol) for 1.3 h. The mixture was concentrated under reduced pressure and purified by flash chromatography (cyclohexane/ethyl acetate, 9:1→8:2) to provide isomer **48a** (76 mg, 38%) as a colorless resin, which was crystallized from cyclohexane; m.p. 78–79 °C; $[\alpha]_D^{25}$ = +33 (*c* = 2, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.90 (m, 1 H, 5-H), 5.79 (m, 2 H, 6-H and C*H*=CH$_2$), 5.05 (m, 2 H, CH=C*H*$_2$), 4.75 (q, *J* = 5.1 Hz, 1 H, 3-H), 4.26 (dd, *J* = 10.6, 5.2 Hz, 1 H, 1-H), 4.17 (m, 4 H, 10a-H and C*H*$_2$CH$_3$), 3.56 (m, 2 H, 1-H and 8a-H), 3.29 (m, 2 H, 7-H and 4a-H), 3.02 (′t′, *J* = 6.5 Hz, 1 H, 8-H), 2.90 (m, 1 H, 4b-H), 1.37 (d, *J* = 5.0 Hz, 3 H, 3-Me), 1.26 (t, *J* = 7.1 Hz, 3 H, CH$_2$C*H*$_3$) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.1, 170.5, 138.9, 129.0, 125.6, 116.2, 99.9, 78.5, 70.1, 67.9, 61.3, 45.2, 41.2, 38.8, 35.6, 20.3, 14.2 ppm. IR (film on NaCl): ṽ = 3082, 3036, 2982, 2874, 1732, 1635, 1465, 1446, 1411, 1373, 1265, 1141, 1087, 1037, 918, 898 cm^{-1}. HRMS (ESI$^+$): *m*/*z* [M + H$^+$] calcd. for $C_{17}H_{23}O_6$ 323.1489; found 323.1489.

Ethyl (+)-(3*R*,4a*S*,4b*R*,7*S*,8*R*,8a*R*,10a*R*)-3,5-Dimethyl-7-vinyl-9-oxo-1,4a,4b,7,8,8a,9,10a-octahydro-2,4,10-trioxaphenanthrene-8-carboxylate (49a): A solution of substrate **37** (100 mg, 0.3 mmol) in anhydrous toluene (3 mL) was heated in a sealed tube at 200 °C in the presence of BHT (13 mg, 0.06 mmol) for 3 h. The mixture was concentrated under reduced pressure and purified by flash chromatography (cyclohexane/ethyl acetate, 9:1→8:2) to provide isomer **49a** (70 mg, 70%) as a colorless resin and a contaminated fraction of isomer **49b** (ca. 6% according to NMR analysis).

Isomer 49a: $[\alpha]_D^{25}$ = +88 (*c* = 1, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.81 (m, 1 H, C*H*=CH$_2$), 5.49 (m, 1 H, 6-H), 5.01 (m, 1 H, CH=C*H*$_2$), 4.97 (m, 1 H, CH=C*H*$_2$), 4.74 (q, *J* = 5.0 Hz, 1 H, 3-H), 4.26 (dd, *J* = 10.8, 5.1 Hz, 1 H, 1-H), 4.14 (m, 4 H, 10a-H and C*H*$_2$CH$_3$), 3.55 (m, 2 H, 1-H and 8a-H), 3.38 (m, 2 H, 7-H and 4a-H), 3.19 (′t′, *J* = 5.3 Hz, 1 H, 8-H), 2.83 (′t′, *J* = 9.4 Hz, 1 H, 4b-H), 1.82 (s, 3 H, 5-Me), 1.36 (d, *J* = 5.1 Hz, 3 H, 3-Me), 1.24 (t, *J* = 7.1 Hz, 3 H, CH$_2$C*H*$_3$) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.8, 170.7, 139.6, 134.0, 123.8, 115.4, 99.5, 78.8, 69.5, 67.9, 61.1, 44.5, 41.0, 39.1, 38.8, 22.8, 20.3, 14.1 ppm. IR (KBr): ṽ = 2978, 2939, 2920, 2870, 1735, 1635, 1446, 1411, 1373, 1265, 1234, 1184, 1165, 1134, 1118, 1091, 1045, 918, 898, 848 cm^{-1}. HRMS (ESI$^+$): *m*/*z* [M + H$^+$] calcd. for $C_{18}H_{25}O_6$ 337.1645; found 337.1659.

Ethyl (–)-(3*R*,4a*S*,4b*R*,7*R*,8*R*,8a*R*,9*R*,10a*R*)-3,7-Dimethyl-9-hydroxy-1,4a,4b,7,8,8a,9,10a-octahydro-2,4,10-trioxaphenanthrene-8-carboxylate (50): A solution of L-Selectride (1 M in THF, 270 μL, 0.27 mmol) was added at –78 °C to a solution of the cycloadduct **47a** (76 mg, 0.25 mmol) in THF (2.7 mL). After 30 min, the reaction was neutralized with a saturated solution of NH_4Cl (1.5 mL) and the mixture was extracted with diethyl ether (2 × 4 mL). The organic extract was washed with brine (1.5 mL), dried with magnesium sulfate, filtered and concentrated to dryness. Purification by silica gel chromatography (cyclohexane/ethyl acetate, 9:1→7:3) afforded compound **50** (76 mg, quantitative yield) as a colorless solid, which was crystallized from cyclohexane; m.p. 147–148 °C; $[\alpha]_D^{25}$ = –178 (*c* = 1.08, MeOH). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.86 (dd, *J* = 10.0, 5.0 Hz, 1 H, 5-H), 5.71 (dd, *J* = 10.0, 4.7 Hz, 1 H, 6-H), 5.25 (s, 1 H, 9-H), 4.67 (q, *J* = 5.0 Hz, 1 H, 3-H), 4.13 (m, 2 H, C*H*$_2$CH$_3$), 4.00 (m, 2 H, 10a-H and 1-H), 3.43 (m, 1 H, 1-H), 3.21 (dd, *J* = 10.9, 8.9 Hz, 1 H, 8-H), 2.94 (dd, *J* = 13.3, 6.0 Hz, 1 H, 4a-H), 2.70 (m, 2 H, 7-H and 8a-H), 2.37 (dd, *J* = 13.3, 5.6 Hz, 1 H, 4b-H), 1.32 (d, *J* = 5.0 Hz, 3 H, 3-Me), 1.26 (t, *J* = 7.1 Hz, 3 H, CH$_2$C*H*$_3$), 1.88 (d, *J* = 7.1 Hz, 3 H, 7-Me) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.6, 131.9, 125.7, 100.0, 93.3, 80.8, 60.5, 68.9, 60.5, 41.9, 35.6, 33.5, 32.0, 20.4, 17.0, 14.2 ppm. IR (KBr): ṽ = 3366, 2970, 2918, 2886, 2860, 1720, 1467, 1389, 1375, 1309, 1282, 1123, 1101, 1087, 1057, 1028, 986, 950, 905 cm^{-1}. HRMS (ESI$^+$): *m*/*z* [M + Na$^+$] calcd. for $C_{16}H_{24}O_6Na$ 335.1471; found 335.1468.

(1*S*,3a*R*,4*R*,5*R*,7a*R*,1′*R*)-1-(1′,2′-Dihydroxyethyl)-5-methyl-3-oxo-1,3,3a,4,5,7a-hexahydroisobenzofuran-4-carboxylate Ethyl Ester (51): Cycloadduct **47a** (3 g, 9.7 mmol) was dissolved in a solution

of TFA (50 mL) and H_2O (50 mL) and the mixture was heated at 80 °C for 30 min. The mixture was then poured into a vigorously stirred saturated solution of $NaHCO_3$ and extracted with CH_2Cl_2 (3 × 40 mL). The organic extract was dried with magnesium sulfate, filtered and concentrated to dryness. Purification by silica gel chromatography (dichloromethane/methanol, 99:1→95:5) afforded **51** (1.83 g, 67%) and acetal **52** (520 mg, 17%, 3:1 diastereomeric mixture) as colorless resins. The α isomer **52** crystallized from cyclohexane.

Compound 51: $[\alpha]_D^{25}$ = –35.7 (*c* = 0.08, MeOH). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.9 (m, 1 H, 7-H), 5.71 (m, 1 H, 6-H), 4.42 (dd, *J* = 9.7, 6.3 Hz, 1 H, 1-H), 4.16 (m, 2 H, C*H*$_2$CH$_3$), 3.92 (m, 1 H, 2′-H), 3.80 (m, 2 H, 1′-H and 2′-H), 3.51 (m, 1 H, 7a-H), 3.23 (dd, *J* = 5.8, 2.1 Hz, 1 H, 4-H), 3.16 (dd, *J* = 7.6, 2.6 Hz, 1 H, 3a-H), 2.53 (m, 1 H, 5-H), 1.92 (br. s, 2 H, OH), 1.26 (t, *J* = 7.1 Hz, 3 H, CH$_2$C*H*$_3$), 1.12 (d, *J* = 7.5 Hz, 3 H, 5-Me) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 176.3, 172.0, 134.8, 121.9, 80.0, 69.6, 63.9, 60.6, 42.4, 42.1, 36.2, 27.9, 18.2, 14.2 ppm. IR (KBr): $\tilde{\nu}$ = 3412, 3034, 2963, 2935, 2937, 2880, 1775, 1466, 1377, 1180, 1129, 1099, 1065, 1026, 1008. HRMS (ESI$^+$): *m*/*z* [M + H$^+$] calcd. for $C_{14}H_{21}O_6$ 285.1332; found 285.1326.

Compound α-52: M.p. 96–97 °C; $[\alpha]_D^{25}$ = –68.3 (*c* = 1.09, MeOH). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.85 (dt, *J* = 10.5, 2.8 Hz, 1 H, 7-H), 5.68 (m, 1 H, 6-H), 5.02 (q, *J* = 4.7 Hz, 1 H, C*H*CH$_3$), 4.29 (dd, *J* = 8.9, 5.9 Hz, 1 H, 1-H), 4.10 (m, 4 H, CH$_3$C*H*$_2$, 2′-H and 1′-H), 3.94 (m, 1 H, 2′-H), 3.45 (m, 1 H, 7a-H), 3.20 (dd, *J* = 6.3, 2.7 Hz, 1 H, 4-H), 3.16 (dd, *J* = 7.5, 2.7 Hz, 1 H, 3a-H), 2.50 (m, 1 H, 5-H), 1.38 (d, *J* = 4.7 Hz, 3 H, CHC*H*$_3$), 1.26 (t, *J* = 7.2 Hz, 3 H, C*H*$_3$CH$_2$), 1.10 (d, *J* = 7.5 Hz, 3 H, 5-Me) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 176.0, 171.9, 134.6, 122.0, 102.3, 81.7, 73.6, 68.6, 60.5, 42.3, 42.0, 36.2, 27.8, 19.9, 18.2, 14.2 ppm. IR (KBr): $\tilde{\nu}$ = 3036, 2990, 2976, 2933, 2910, 2877, 1767, 1728, 1418, 1373, 1335, 1242, 1179, 1151, 1130, 1117, 1088, 1036, 1022, 999, 962, 869 cm^{-1}. HRMS (ESI$^+$): *m*/*z* [M + H$^+$] calcd. for $C_{16}H_{23}O_6$ 311.1489; found 311.1486.

Supporting Information (see footnote on the first page of this article): Experimental details for the synthesis of molecules **5**–**37**, X-ray data for **47b**, **50**, α-**52**, and copies of ^{1}H and ^{13}C NMR spectra for all compounds.

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