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Diels-Alder Reactions

Selectivity in the Intermolecular Diels–Alder Reaction of Conjugated Trienes: Experimental and Theoretical Approaches

Camille Remeur,[a] Sandy Desrat,[a] Vincent Gandon,[a,b] and Fanny Roussi*[a]

Abstract: Eleven analogs of the natural product meiogynin A, an inhibitor of proteins of the Bcl-2 family, have been elaborated by an intermolecular Diels–Alder (DA) reaction of various conjugated chloro-trienes, in order to determine the influence of the modification of the south part of meiogynin A on its biological activity. The chloro-trienes were obtained in two to five steps from commercial compounds through a selective hydrochlorination of bromoalkyne intermediates to (*Z*)-1,2-dihalogenated alkenes followed by a chemoselective Suzuki–Miyaura cross-coupling. The intermolecular DA reaction of these trienes with two α,β-unsaturated carboxylic acids as dienophiles occurred with a perfect regioselectivity and good to excellent diastereoselectivities. These selectivities could be rationalized by DFT calculations.

Introduction

The Diels–Alder reaction is one of the most powerful and versatile reactions in organic chemistry. This cyclization process enables the straightforward elaboration of complex molecules in a single operation through the simultaneous formation of two carbon–carbon[1] and/or carbon–heteroatom bonds.[2] Thus, it comes as no surprise that such a simple but efficient reaction is highly pertinent in natural product synthesis as well as in the preparation of various medicinally relevant molecules.[1]

Among the various possible diene/dienophile combinations, Diels–Alder processes involving conjugated trienes as dienes have only been sporadically reported, mainly by intramolecular Diels–Alder (IMDA) or transannular Diels–Alder (TADA) approaches. Examples include syntheses by Roush and co-workers of superstolide A[3] and spinosyne A,[4] Baldwin's elaboration of spiculoic acid through a highly elegant biomimetic approach,[5] and Kishi's synthesis of gymnodimine.[6] Recently, studies on the synthesis of chaetochalasin A by using IMDA reaction of a triene was also disclosed.[7] The same synthetic strategy has also been utilized in the preparation of antimicrobial agents such as in the enantioselective synthesis the GKK1032s core by Inoue.[8] Intermolecular Diels–Alder (DA) of conjugated trienes used as dienes is much less documented in the literature likely because of inherent problems with regiochemical fidelity. However, intermolecular variants have been successfully employed by Stork in 1977 for his impressive synthesis of cytochalasin B[9] and by Roush for the elegant synthesis of (–)-chlorothricolide.[10]

Our team successfully exploited this approach for the bioinspired total synthesis of meiogynin A **5**,[11] a dimeric sesquiterpenoid isolated from the bark of a Malaysian tree,[12] which has been identified as a natural inhibitor of proteins of the Bcl-2 family. These antiapoptotic proteins are involved in the programmed cell death (PCD) and are overexpressed in various cancers, which render them interesting targets for cancer treatment.[13] Due to the relevant biological properties of meiogynin A and to its unique structure, several modifications have been explored, mainly on the lateral chain, and in doing so, highly potent unnatural analogues have been elaborated.[14] The general synthetic strategy to obtain these compounds relied on an organocatalytic intermolecular DA cycloaddition between various trienes (**1**, **7**, **11** and **12**) and three α,β-unsaturated carboxylic acids (**3a–b** and **8**) as dienophiles (Scheme 1). The *o*-bromophenylboronic acid catalyst **2** was assumed to provide activation, by a LUMO-lowering effect, of dienophiles through the formation of a covalent monoacylated hemiboronic intermediate **4**.[15] Unsurprisingly, the yield of the reaction and the reactivity of the trienes were greatly influenced by their nature: native triene **1**[11] was much more reactive than conjugated triene alcohol **7**[14a,14c] for which 8 to 15 days were required for completion of the reaction whereas conjugated triene acid **11** was totally unreactive.[14a] Gratifyingly, the installation of a chlorine atom in the vinylic position (compound **12**) could restore the reactivity of the triene and boosted the reaction (2 days), probably by raising the HOMO energy level of the reacting external diene thanks to mesomeric effects of halide atom.[14d]

In this paper, we wish to report on the intermolecular DA of chlorotrienes substituted on their phenyl ring at different positions. The objective of this work was to gain additional experimental insight into the reactivity of conjugated trienes and into the observed selectivity, supported by DFT calculations. Moreover, the products prepared for this study allowed us to

[a] *Institut de Chimie des Substances Naturelles, CNRS-ICSN UPR 2301, Université Paris-Saclay, Avenue de la Terrasse, 91198 Gif-sur-Yvette Cedex, France*
E-mail: fanny.roussi@cnrs.fr
http://www.icsn.cnrs-gif.fr/spip.php?article587
[b] *ICMMO, CNRS UMR 8182, Univ Paris-Sud, Université Paris-Saclay, Bât. 420, 91405 Orsay cedex, France*
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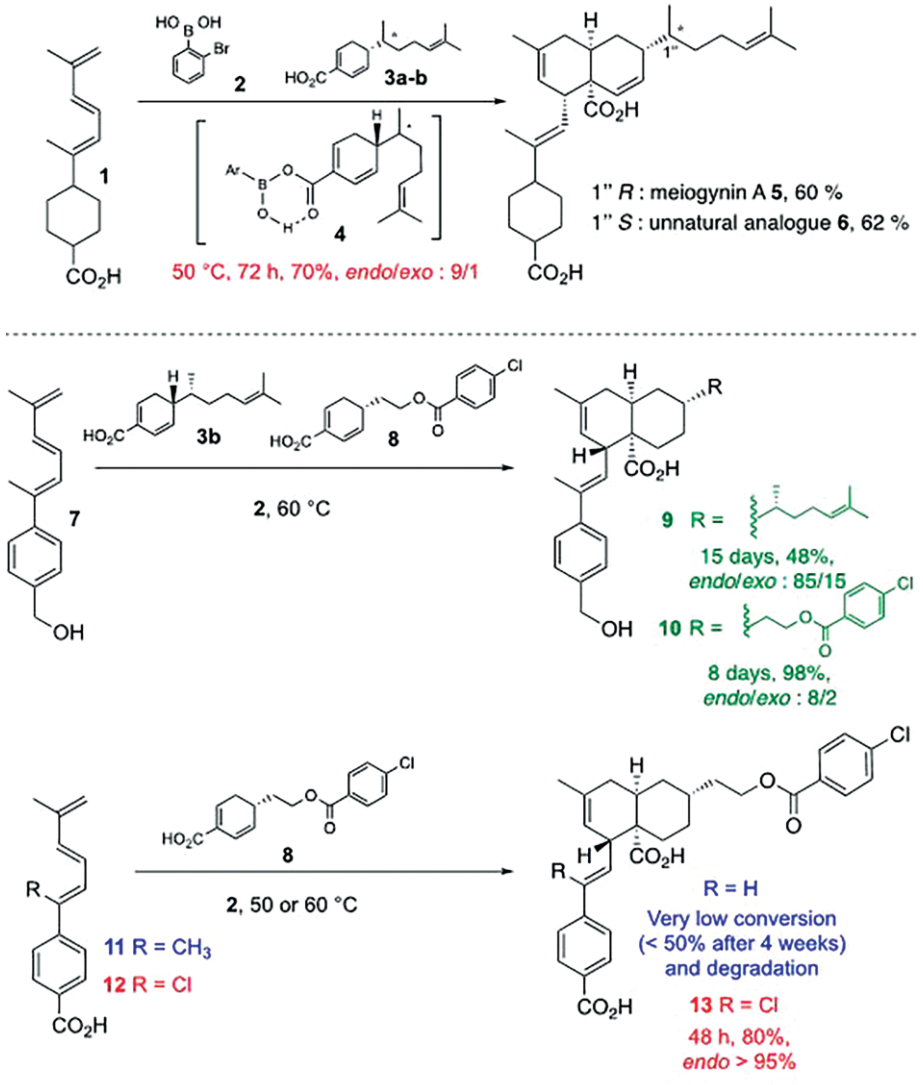


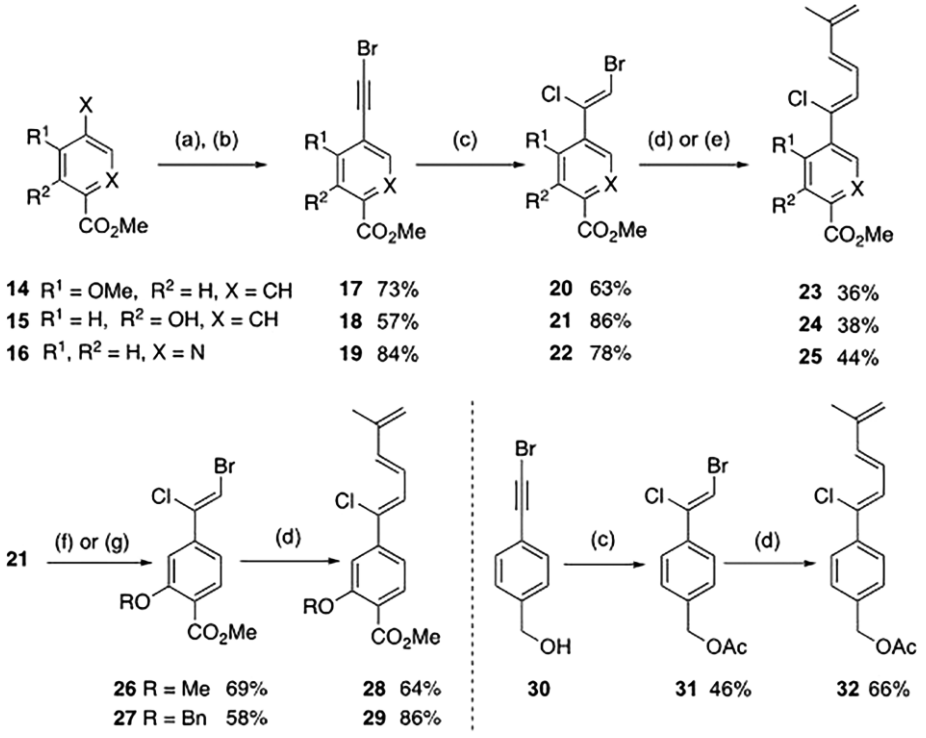
Scheme 1. Observed selectivity in the intermolecular Diels–Alder reaction of conjugated trienes.

determine the influence of the modification of the south part of meiogynin A on its biological activity.

Results and Discussion

To access the requisite chloro-trienes, we designed a short synthesis in which the final step was a Suzuki coupling between a dienyl boronic ester and different (*Z*)-4-(2-bromo-1-chlorovinyl)phenyl or pyridinyl derivatives. In the literature, preparation of such (*Z*)-1,2-alkenes is not straightforward, unlike the elaboration of their *trans* counterparts. In this regard, in 2012, the Zhu group reported on an elegant approach to (*Z*)-1,2-dihalogenated alkenes by a stereoselective palladium-catalyzed hydrohalogenation of haloalkynes.[16] This very efficient and selective method was employed to prepare various *Z*-4-(2-bromo-1-chlorovinyl)phenyl or pyridinyl intermediates **20**–**22** and **31**. The requisite bromo-alkynes **17** and **19** could be obtained in two steps starting from commercial aryl halides **14** and **16** by a Sonogashira coupling followed by a one-pot desilylation/bromination sequence using AgF as the Ag^{I} source.[17] Alternatively, as the one-pot desilylation/bromination sequence was unsuccessful, intermediate **18** was elaborated in three steps.

Hydrochlorination of bromoalkynes **17**–**19** and **30** was then performed, using the conditions described by Zhu, i.e. $[(allyl)PdCl]_2$ as the catalyst and *cis*,*cis*-1,5-cyclooctadiene as the ligand.[16] This robust protocol provided the expected (*Z*)-4-(2-bromo-1-chlorovinyl)phenyl or pyridinyl derivatives **20**–**22** in very good yields with excellent regio- and stereoselectivity. Compound **21** could be further derivatized by introduction of a methyl or a benzyl group on the phenol function in order to probe the role of steric hindrance in the *ortho* position to the carboxylate group in SAR studies. Interestingly, the hydrochlorination of compound **30** run in acetic acid afforded predominately the benzyl acetate **31**. Finally, the desired trienes **23**–**25**, **28**, **29**, **32** were obtained directly from these dihalogenated alkenes via chemoselective Suzuki coupling with (*E*)-4,4,5,5-tetramethyl-2-(3-methylbuta-1,3-dien-1-yl)-1,3,2-dioxaborolane.[11] Complete selectivity was observed when attempting



Scheme 2. Preparation of triene esters. Reagents and conditions: (a) (triisopropylsilyl)acetylene, Pd[$(PPh_3)_2Cl_2$] (5 mol-%), CuI (0.5 equiv.), Et_3N, room temp., 24 h (for **14**, **15**) or Et_3N/THF (1:1), 60 °C, 18 h (for **16**); (b) NBS (1.2 equiv.), AgF (1.2 equiv.), CH_3CN, room temp. (for **14** and **16**) or TBAF (1.2 equiv.), THF, room temp. then NBS (1.2 equiv.), $AgNO_3$ (10 mol-%), acetone, room temp. for (**15**); (c) $[(allyl)PdCl]_2$ (2.5 mol-%), LiCl (2.0 equiv.), *cis*,*cis*-1,5-cyclooctadiene (10 mol-%), AcOH, 80 °C, 18 h; (d) (*E*)-4,4,5,5-tetramethyl-2-(3-methylbuta-1,3-dien-1-yl)-1,3,2-dioxaborolane (3.0 equiv.), $Pd(PPh_3)_4$ (5 mol-%), K_3PO_4 (4.0 equiv.), THF/H_2O (2:1), 50 °C, 8 h (for **20**, **21**, **26**, **27**); (e) (*E*)-4,4,5,5-tetramethyl-2-(3-methylbuta-1,3-dien-1-yl)-1,3,2-dioxaborolane (3.0 equiv.), $Pd(PPh_3)_4$ (5 mol-%), Cs_2CO_3 (4.0 equiv.), THF, reflux, 12 h (for **22**); (f) Me_2SO_4 (1.5 equiv.), K_2CO_3 (3.0 equiv.), acetone, reflux; (g) BnCl (1.0 equiv.), NaH (1.2 equiv.), DMF.

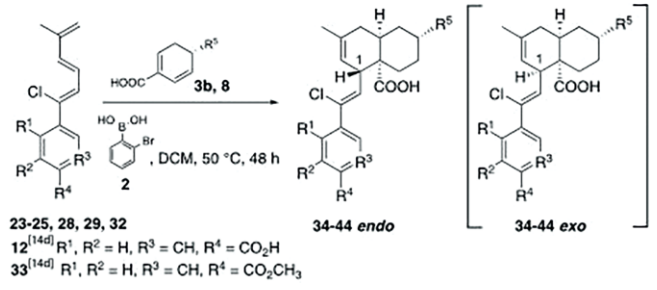
chemoselective cross coupling. Nearly all trienes were obtained in moderate to good yields when using K_3PO_4 as a base. An exception was noticed for compound **25**, which required Cs_2CO_3. In the presence of this base, compound **25** could be obtained in acceptable yield of 44 % (Scheme 2).

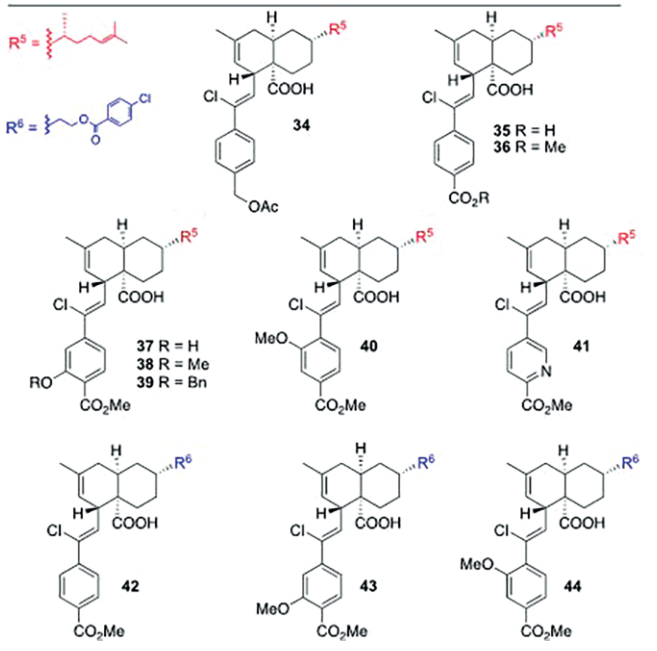
Attempts to engage all prepared trienes in regio-specific Diels–Alder cycloaddition were next initiated using both dienophiles **3b** and **8** and trienes **12**, **23**–**25**, **28**, **29**, **32**, **33**[14d] (Table 1). Based on literature reports and on our previous results, we elected to use a sub-stoichiometric amount of 2-bromophenylboronic acid **2**, hypothesized to lower the LUMO energy of the acrylate dienes **3b** and **8** thus enhancing their ability to react in the cycloaddition process.[15] Pleasingly, all trienes underwent a regio-selective cycloaddition to furnish compounds **34**–**44** as a *endo*/*exo* inseparable mixture, mostly in 48 h under mild conditions. On the one hand, no traces of the other possible regioisomers arising from a cycloaddition on different positions of the trienes or of dienophiles **3b** and **8** could be detected in crude mixtures. With dienophile **3b**, good diastereoselectivities were measured, with *endo*/*exo* ratios of about 85:15. On the other hand, yields greatly depended on the nature of the trienes. Indeed, high yields were obtained for compounds **34**–**38** and **41** but compounds **39** and **40** were obtained in very low yields, accompanied by polymerized trienes **23** and **29** after 6 days of reaction. From dienophile **8**, cycloadduct **42** was isolated in excellent yield whereas **43** and **44** were obtained in lower yield, accompanied by polymerized triene **28**. *Cis*-decalins **42** and **43** were obtained with 95 % diastereoselectivity in favour of the *endo* products while *endo*/*exo* ratio observed for compound **44** was much lower (80:20). Unfortunately, none of the cycloadducts were as active as natural meiogynin A and previous developed derivatives[14] with in vitro affinity displacement assays based on the modulation of Bcl-xL/Bak and Mcl1/Bid interactions. These results indicated that modulation of the south part of this family of compounds is useless or detrimental for their activities.

In order to explain the observed reactivities in the Diels–Alder reaction of these conjugated trienes, DFT calculations were performed. All structures (minima and transition states) were optimized using the Gaussian 09 software package,[18] at the M06–2X/6-311+G(d,p)// level of theory.[19,20] The value presented herein are Gibbs free energies (ΔG_{298}, kcal/mol). Triene **12**, named **A** below, was used in the computations without simplifications (Scheme 3). The monoacylated hemiboronic compound **B**, exhibiting a *para* isopropyl substituent was used as model Diels–Alder partner. The cycloadducts **C** and **C′** are expected from *endo* and *exo* [4+2] cycloadditions respectively, taking place at the terminal diene framework of **A**.

Endo and *exo* cycloadditions could be modelled from **A** and **B** to give **C** and **C′** (Figure 1). Both were concerted asynchronous processes during which the first C–C bond formed involves the less substituted carbons of the two partners. The *endo* cycloaddition is clearly favored over the *exo* one, by 4.3 kcal/mol.[21] Analysis of the secondary orbital interactions is

Table 1. Diels Alder reactions of trienes **12**, **23**–**25**, **28**, **29**, **32** and **33**.[a]



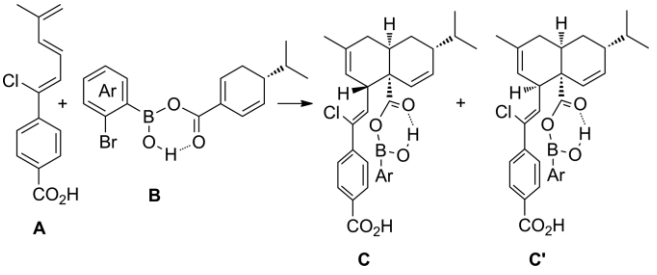


Entry	Product	*endo*/*exo* ratio[b]	Yield [%][c]
1	**34**	85:15	87
2	**35**	80:20	62
3	**36**	80:20	73
4	**37**	85:15	59
5	**38**	90:10	47
6	**39**	80:20	14[d]
7	**40**	80:20	< 10[d,e]
8	**41**	90:10	60
9	**42**	> 95:5	96
10	**43**	> 95:5	37[e]
11	**44**	80:20	55[e]

[a] Reagents and conditions: compound **3b** or **8**, 2-bromophenylboronic acid (30 mol-%), CH_2Cl_2, 50 °C, 48 h. [b] Determined by integration of the signals on the ^{1}H NMR spectra of the crude mixture. [c] Isolated yield (*endo*/*exo* mixture). [d] After 6 days of reaction. [e] Compound not isolated: yield was estimated according to the ^{1}H NMR spectra of the crude mixture.

presented in the Supporting Information. The two reactions are exergonic by ca. 13 kcal/mol, with a slight 0.6 kcal/mol preference for **C**.

Of note, the cycloaddition takes place in each case *anti* to the *i*Pr group. The *endo* mode could be computed on the *i*Pr face. The *exo* one could also be, but the corresponding free energy of activation is 0.5 kcal/mol higher than the previously computed one (25.3 kcal/mol). Manifold efforts failed to locate a cycloaddition transition state that would involve the internal



Scheme 3. Diels–Alder cycloaddition between triene **A** and simplified dienophile **B** studied by DFT computations.

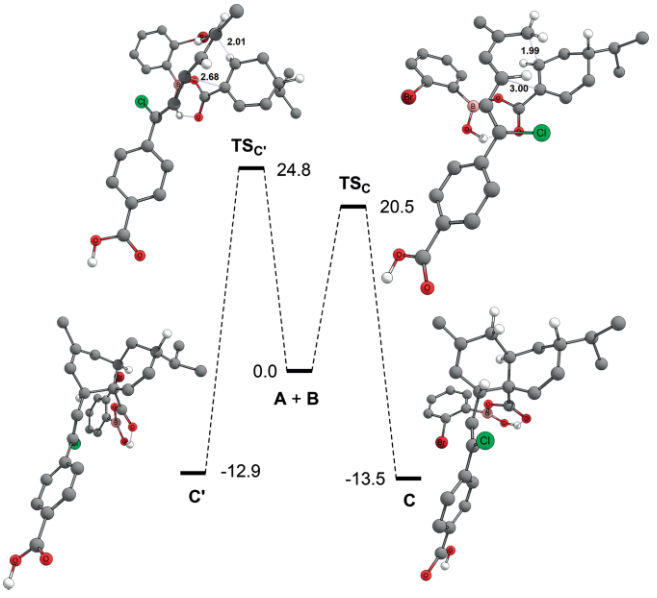


Figure 1. Reaction profile (ΔG_{298}, kcal/mol) and geometries of computed transition states and adducts (selected distances in Å, some hydrogen atoms have been omitted for clarity).

diene framework of **A** instead of the external one. It was also not possible to locate a transition state corresponding to the addition of the external triene carbon into the most hindered alkene carbon of **B**, nor to the disubstituted alkene framework of **B**. These computational failures are actually consistent with the experimental results and show that this kind of cycloaddition is very sensitive to the steric hindrance of the two partners. In addition, frontier orbital analysis of **A** and **B** indicate that the largest coefficients are located where the cycloaddition actually takes place experimentally (Figure 2).

Additional calculations were carried out to evaluate the influence of the chlorine and of the carboxylic acid group on the triene in hypothetical *endo* cycloadditions *anti* to the *i*Pr group (see the Supporting Information). Without the chlorine atom, **TSc** reaches 21.8 kcal/mol, which is quite close from the 20.5 value obtained previously (see Figure 1). With the chlorine atom but without the CO_2H group, the barrier is lowered to 19.0 kcal/mol. In the absence of the two, it further lowers to 18.9 kcal/mol. Thus, the cyclization barriers are in a narrow range of 2.9 kcal/mol depending on the substitution pattern, which plays a limited role. The uncatalyzed process was also com-

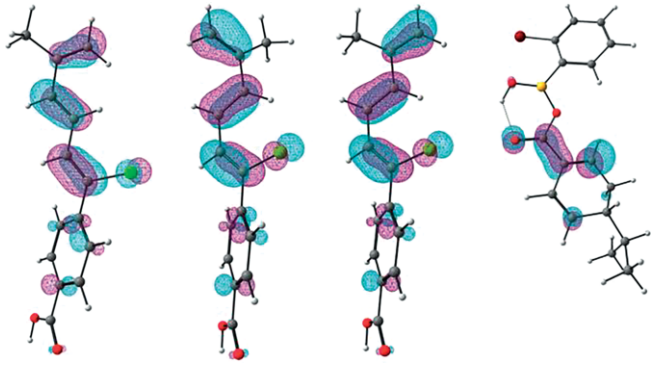


Figure 2. HOMO of *s-cis/s-trans* **A** (left), of *s-cis/s-cis* **A** (center left), of *s-trans/s-cis* **A** (center right), and LUMO of **B** (right) at a contour value of 0.05.

puted. In this case, the [4+2] cycloaddition barrier is significantly increased to 25.3 kcal/mol, as compared to the previously computed value of 20.5 kcal/mol for the catalyzed process.

Conclusions

To summarize, we presented an elegant and straightforward strategy to access eleven new analogues of meiogynin A from six functionalized conjugated trienes, with a perfect regioselectivity and good to excellent diastereoselectivities. DFT computations have highlighted that this DA reaction is an asynchronous process. Its regioselectivity was rationalized by steric factors and *endo* selectivity by a more favorable transition state. Finally, we could demonstrate that the introduction of a chlorine atom at a strategic position could increase notably the reactivity of the trienes, thus the yield of these reactions.

Experimental Section

General Experimental Procedures: All reagents and solvents were used as purchased from commercial suppliers or were purified/dried according to Armarego and Chai.[22] The 2-bromophenylboronic acid catalyst **2** was used as received. Purifications by column chromatography on silica gel were performed using Merck Silica Gel 60 (70–230 mesh). ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AC300 or ARX500 instruments using $CDCl_3$, MeOD or [D_6]acetone with trace of non-deuterated residual solvents used as a internal references. Chemical shifts are given in parts per million (ppm), and multiplicity of signals are reported as follows: s, singlet; br. s, broad singlet; d, doublet; t, triplet; q, quartet; dd, doublet of doublets; m, multiplet. HRMS analyses were obtained using a Waters LCT Premier instrument by ElectroSpray, Ionization (ESI) or by Atmospheric Pressure Photo-Ionization (APPI). Melting points were measured with a Büchi Melting Point B-540 apparatus. Optical rotation, $[\alpha]_D^{20}$ values, were measured using an Anton Paar MCP 300 instrument and are expressed in deg cm^3 g^{-1} dm^{-1} for a concentration of compound in g/cm^{-1}. IR spectra were recorded on a Perkin–Elmer Spectrum BX-FTIR spectrometer.

Methyl 4-(Bromoethynyl)-3-methoxybenzoate (17): To a solution of commercial methyl 4-iodo-3-methoxybenzoate 4 (280 mg, 0.96 mmol), copper iodide (91 mg, 0.48 mmol, 0.5 equiv.), and bis(triphenylphosphine)palladium(II) dichloride (33 mg, 0.048 mmol, 0.05 equiv.) in Et_3N (2.5 mL) under argon, was added dropwise (triisopropylsilyl)acetylene (0.22 mL, 1.01 mmol, 1.05 equiv.). After 18 h at room temp., the reaction mixture was quenched with a saturated solution of NH_4Cl and the product was extracted with MTBE (three times). The combined organic phases were dried with $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by chromatography on silica gel using heptane/ethyl acetate (10 to 9:1) to give methyl 3-methoxy-4-[(triisopropylsilyl)ethynyl]benzoate as a yellow oil (270 mg, 0.78 mmol, 82 %). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.56 (dd, J = 7.9, 1.5 Hz, 1 H), 7.51 (d, J = 1.4 Hz, 1 H), 7.47 (d, J = 7.9 Hz, 1 H), 3.91 (s, 3 H), 3.88 (s, 3 H), 1.1 (s, 21 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.9, 160.8, 133.9, 131.1, 121.8, 118.0, 111.7, 102.6, 99.0, 56.3, 52.6, 18.9 (6 C), 11.6 (3 C) ppm. IR : $\tilde{\nu}$ = 3675, 2943, 2153, 1721, 1284, 1036, 668 cm^{-1}. HRMS (ESI) m/z calcd. for $C_{20}H_{31}O_3Si$ [M + H]$^+$ 347.2037, found 347.2050.

To a solution of 3-methoxy-4-[(triisopropylsilyl)ethynyl]benzoate (396 mg, 1.14 mmol) in dry acetonitrile (32 mL), were added *N*-bromosuccinimide (244 mg, 1.37 mmol, 1.2 equiv.) and silver fluoride (174 mg, 1.37 mmol, 1.2 equiv.) under argon. After 3 h at room temp. in the dark, the reaction mixture was filtered through a pad of Celite® and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel using heptane/ethyl acetate (10 to 8:2) to give methyl 4-(bromoethynyl)-3-methoxybenzoate **17** as a white powder (274 mg, 1.02 mmol, 89 %). Compound **17**: M.p. 118–119 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.57 (dd, J = 7.9, 1.5 Hz, 1 H), 7.52 (d, J = 1.4 Hz, 1 H), 7.46 (d, J = 7.9 Hz, 1 H), 3.93 (s, 3 H), 3.91 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.7, 160.8, 134.1, 131.6, 121.9, 116.9, 111.6, 76.2, 56.7, 56.3, 52.6 ppm. IR: $\tilde{\nu}$ = 2946, 2194, 1711, 1403, 1289, 1108, 869, 757 cm^{-1}. HRMS (ESI) m/z calcd. for $C_{11}H_{10}BrO_3$ [M + H]$^+$ 268.9808, found 268.9821.

Methyl 4-(Bromoethynyl)-2-hydroxybenzoate (18): To a solution of commercial methyl 4-iodosalicylate (2 g, 7.19 mmol), copper iodide (0.68 g, 3.60 mmol, 0.5 equiv.), and bis(triphenylphosphine)palladium(II) dichloride (0.25 g, 0.36 mmol, 0.05 equiv.) in Et_3N (20 mL) under argon, was added dropwise (triisopropylsilyl)acetylene (1.70 mL, 7.55 mmol, 1.05 equiv.). After 18 h at room temp., the reaction mixture was quenched with a saturated solution of sodium hydroxide and the product was extracted with MTBE (three times). The combined organic phases were dried with $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by chromatography on silica gel using heptane/ethyl acetate (10 to 9:1) to give methyl 2-hydroxy-4-[(triisopropylsilyl)ethynyl]-benzoate as an orange powder (2.34 g, 7.04 mmol, 98 %). Mp 54–56 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 10.72 (s, 1 H), 7.75 (d, J = 8.1 Hz, 1 H), 7.08 (d, J = 1.6 Hz, 1 H), 6.96 (dd, J = 8.1, 1.6 Hz, 1 H), 3.94 (s, 3 H), 1.12 (s, 21 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.4, 161.5, 131.0, 130.0, 123.0, 121.2, 112.4, 106.1, 95.0, 52.7, 18.9 (6 C), 11.6 (3 C) ppm. IR: $\tilde{\nu}$ = 3156, 2954, 2864, 2159, 1664, 1443, 1213, 869, 781 cm^{-1}. HRMS (ESI) m/z calcd. for $C_{19}H_{29}O_3Si$ [M + H]$^+$ 333.1880, found 333.1891.

TBAF (1 M in THF) was added dropwise to a solution of methyl 2-hydroxy-4-[(triisopropylsilyl)ethynyl]benzoate (0.5 g, 1.5 mmol) in dry THF (3 mL) under argon. After 5 h at room temp., the reaction mixture was quenched with a saturated solution of NH_4Cl and the product was extracted with MTBE (three times). The combined organic phases were dried with $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by chromatography on silica gel using heptane/ethyl acetate (10 to 9:1) to give methyl 4-ethynyl-2-hydroxybenzoate as an orange powder (0.20 g, 1.15 mmol, 76 %). Mp 194–195 °C (decomposition). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 10.74 (s, 1 H), 7.78 (d, J = 8.2 Hz, 1 H), 7.10 (d, J = 1.6 Hz, 1 H), 7.02 (dd, J = 8.2, 1.5 Hz, 1 H), 3.95 (s, 3 H), 3.20

(s, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.2, 161.4, 130.3, 128.8, 123.4, 121.7, 113.5, 81.9, 76.5, 52.8 ppm. IR: $\tilde{\nu}$ = 3155, 2952, 1676, 1439, 1198, 742, 686 cm^{-1}.

To a solution of methyl 4-ethynyl-2-hydroxybenzoate (530 mg, 3.01 mmol) in acetone (24 mL) were added NBS (643 mg, 3.61 mmol, 1.2 equiv.) and $AgNO_3$ (51 mg, 0.30 mmol, 0.1 equiv.). The reaction mixture was stirred, in the dark, at room temp. for 3 h and then filtered through a pad of Celite®. The filtrate was concentrated under reduced pressure and the residue was purified by column chromatography on silica gel using heptane/ethyl acetate (100 to 95:5) to give methyl 4-(bromoethynyl)-2-hydroxybenzoate **18** as a yellow solid (590 mg, 2.33 mmol, 77 %). Compound **18**: Mp 107–109 °C (decomposition). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 10.74 (s, 1 H), 7.76 (d, J = 8.2 Hz, 1 H), 7.05 (d, J = 1.5 Hz, 1 H), 6.93 (dd, J = 8.2, 1.5 Hz, 1 H), 3.94 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.3, 161.5, 130.1, 130.1, 123.0, 121.2, 112.8, 79.5, 53.9, 52.7 ppm. IR: $\tilde{\nu}$ = 3096, 2953, 2191, 1664, 1440, 1213, 781, 690 cm^{-1}. HRMS (ESI) m/z calcd. for $C_{10}H_8BrO_3$ $[M + H]^+$ 254.9651, found 254.9660.

Methyl 5-(Bromoethynyl)picolinate (19): (Triisopropylsilyl)acetylene (6.22 mL, 27.8 mmol, 3 equiv.) was added dropwise to a suspension of commercial methyl 5-bromopicolinate (2.0 g, 9.26 mmol), copper iodide (53 mg, 0.28 mmol, 0.03 equiv.), and bis(triphenylphosphine)palladium(II) dichloride (130 mg, 0.19 mmol, 0.02 equiv.) in Et_3N/THF (60 mL) under argon. After 18 h at 60 °C, the reaction mixture was filtered through a pad of Celite® and concentrated under reduced pressure. The crude mixture was purified by column chromatography on silica gel using heptane/ethyl acetate (10 to 8:2) to give methyl 5-[(triisopropylsilyl)ethynyl]picolinate as a yellow oil (2.91 g, 9.17 mmol, 99 %). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.75 (dd, J = 2.0, 0.8 Hz, 1 H), 8.07 (dd, J = 8.1, 0.8 Hz, 1 H), 7.87 (dd, J = 8.1, 2.0 Hz, 1 H), 4.00 (s, 3 H), 1.11 (s, 21 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.5, 152.7, 146.4, 140.1, 124.6, 124.3, 102.9, 99.1, 53.3, 18.9 (6 C), 11.5 (3 C) ppm. IR: $\tilde{\nu}$ = 3675, 2944, 2865, 2159, 1724, 1307, 1218, 1131, 882, 676 cm^{-1}. HRMS (ESI) m/z calcd. for $C_{18}H_{28}NO_2Si$ $[M + H]^+$ 318.1889, found 318.1874.

To a solution of methyl 5-[(triisopropylsilyl)ethynyl]picolinate (2.91 g, 9.17 mmol) in dry acetonitrile (97 mL), was added, under argon and in the dark, *N*-bromosuccinimide (1.96 g, 11.0 mmol, 1.2 equiv.) and silver fluoride (1.39 g, 11.0 mmol, 1.2 equiv.). After 3 h at room temp., the reaction mixture was filtered through a pad of Celite® and concentrated under reduced pressure. The crude mixture was purified by column chromatography on silica gel using heptane/ethyl acetate (10 to 8:2) to give methyl 5-(bromoethynyl)picolinate **19** as a white powder (1.87 g, 7.79 mmol, 85 %). Compound **19**: Mp: 133–134 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.78 (dd, J = 2.1, 0.7 Hz, 1 H), 8.09 (dd, J = 8.1, 0.8 Hz, 1 H), 7.87 (dd, J = 8.1, 2.1 Hz, 1 H), 4.00 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.4, 152.8, 146.8, 140.2, 124.7, 123.7, 76.7, 57.6, 53.4 ppm. IR: $\tilde{\nu}$ = 3675, 2988, 2197, 1706, 1438, 1311, 1130, 859, 691 cm^{-1}. HRMS (ESI) m/z calcd. for $C_9H_7BrNO_2$ $[M + H]^+$ 239.9655, found 239.9715.

General Procedure for the Hydrochloration Reaction: To a solution of bromo-alkyne **17**–**19**, or **30** and LiCl (2.0 equiv.) in AcOH, were added allylpalladium(II) chloride dimer (2.5 mol-%) and *cis*,*cis*-1,5-cyclooctadiene (10 mol-%). After 18 h at 80 °C, the reaction mixture was cooled down and water was added. The aqueous layer was then extracted with MTBE (three times) and the combined organic phases were washed with a saturated solution of $NaHCO_3$, dried with $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel using a gradient of heptane/ethyl acetate.

Methyl (Z)-4-(2-Bromo-1-chlorovinyl)-3-methoxybenzoate (20): Compound **20** was obtained as an orange amorphous solid (66 mg, 0.22 mmol, 63 %) from compound **17** (93 mg, 0.35 mmol). Compound **20**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.64 (dd, J = 8.0, 1.5 Hz, 1 H), 7.58 (d, J = 1.5 Hz, 1 H), 7.52 (d, J = 7.9 Hz, 1 H), 7.04 (s, 1 H), 3.93 (s, 3 H), 3.90 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.6, 156.7, 133.5, 132.3, 130.6, 130.0, 122.1, 112.4, 110.5, 56.3, 52.7 ppm. IR: $\tilde{\nu}$ = 2951, 1725, 1426, 1225, 874, 755 cm^{-1}. HRMS (ESI) m/z calcd. for $C_{11}H_{11}BrClO_3$ $[M + ACN + H]^+$ 345.9840, found 345.9851.

Methyl (Z)-4-(2-Bromo-1-chlorovinyl)-2-hydroxybenzoate (21): Compound **21** was obtained as a white powder (4.37 g, 14.99 mmol, 86 %) from compound **18** (4.40 g, 17.4 mmol). Compound **18**: Mp 95.4–97.5 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 10.78 (s, 1 H), 7.82 (d, J = 8.5 Hz, 1 H), 7.18 (d, J = 1.9 Hz, 1 H), 7.06 (dd, J = 8.5, 1.9 Hz, 1 H), 3.96 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.2, 161.8, 143.2, 130.5, 120.6, 117.5, 116.1, 113.2, 108.3, 52.8 ppm. IR: $\tilde{\nu}$ = 3187, 1671, 1433, 1209, 1092, 846, 773, 688 cm^{-1}. HRMS (ESI) m/z calcd. for $C_{10}H_9BrClO_3$ $[M + H]^+$ 290.9418, found 290.9429.

Methyl (Z)-5-(2-Bromo-1-chlorovinyl)picolinate (22): Compound **22** was obtained as a white powder (503 mg, 1.82 mmol, 78 %) from compound **19** (560 mg, 2.33 mmol). Compound **22**: Mp 86–87 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.88 (d, J = 2.3 Hz, 1 H), 8.15 (d, J = 8.2 Hz, 1 H), 8.01 (dd, J = 8.2, 2.0 Hz, 1 H), 7.13 (s, 1 H), 4.02 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.3, 148.3, 147.4, 135.3, 134.9, 125.2, 109.6, 53.4 ppm. IR: $\tilde{\nu}$ = 3073, 2953, 1706, 1315, 1123, 765, 700 cm^{-1}. HRMS (ESI) m/z calcd. for $C_9H_8BrClNO_2$ $[M + H]^+$ 275.9421, found 275.9428.

(Z)-4-(2-Bromo-1-chlorovinyl)benzyl Acetate (31): Compound **31** was obtained as a red oil (1.56 g, 5.39 mmol, 47 %) accompanied with 20 % of separable (*Z*)-[4-(2-bromo-1-chlorovinyl)phenyl]methanol from compound **30** (2.41 g, 11.40 mmol). Compound **32**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.53 (d, J = 8.3 Hz, 2 H), 7.36 (d, J = 8.3 Hz, 2 H), 6.88 (s, 1 H), 5.10 (s, 2 H), 2.11 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.0, 138.3, 137.6, 136.6, 128.6 (2 C), 127.1 (2 C), 105.8, 65.8, 21.2 ppm. IR: $\tilde{\nu}$ = 3076, 1735, 1378, 1220, 1018, 770 cm^{-1}. HRMS (ESI) m/z calcd. for $C_{11}H_{11}BrClO_2$ $[M + H]^+$ 288.9625, not found. Compound 12: m.p. 41 – 43 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.53 (d, J = 8.3 Hz, 2 H), 7.36 (d, J = 8.3 Hz, 2 H), 6.87 (s, 1 H), 4.70 (s, 2 H), 1.87 (s, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 142.5, 138.5, 136.1, 127.3 (2 C), 127.1 (2 C), 105.5, 64.9 ppm. IR: $\tilde{\nu}$ = 3241, 3072, 1408, 1217, 1057, 768 cm^{-1}.

Methyl (*Z*)-4-(2-Bromo-1-chlorovinyl)-2-methoxybenzoate (26): To a solution of compound **21** (400 mg, 1.37 mmol) in acetone (13 mL) was added potassium carbonate (570 mg, 4.12 mmol, 3.0 equiv.) followed by dropwise addition of dimethyl sulfate (0.2 mL, 2.05 mmol, 1.5 equiv.). After 2 h of reflux, the reaction mixture was cooled down and quenched with a saturated solution of NH_4Cl. The aqueous phase was extracted with MTBE (3 times). The combined organic phases were dried with $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel using heptane/ethyl acetate (10 to 7:3) to give **26** as a white amorphous solid (280 mg, 0.94 mmol, 69 %). Compound **26**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.78 (d, J = 8.4 Hz, 1 H), 7.14 (d, J = 1.7 Hz, 1 H), 7.13 (dd, J = 8.5, 1.7 Hz, 1 H), 7.00 (s, 1 H), 3.93 (s, 3 H), 3.89 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.2, 159.4, 141.5, 137.8, 132.3, 121.0, 118.6, 110.7, 107.7, 56.4, 52.5 ppm. IR: $\tilde{\nu}$ = 3077, 2916, 1689, 1400, 1294, 1089, 1031, 847, 764 cm^{-1}. HRMS (ESI) m/z calcd. for $C_{11}H_{11}BrClO_3$ $[M + H]^+$ 304.9575, found 304.9571.

Methyl (*Z*)-2-(Benzyloxy)-4-(2-bromo-1-chlorovinyl)benzo-ate (27): To a solution of compound **21** (100 m g, 0.34 mmol), in anhydrous DMF (4 mL) at 0 °C, was added sodium hydride 60 % (14 mg, 0.4 mmol, 1.2 equiv.). After 30 min at 0 °C, *tert*-butylammo-

nium iodide (1.2 mg, 1 mol-%) and benzyl bromide (40 μL, 0.34 mmol, 1 equiv.) were added. After 12 h at room temperature, the reaction mixture was quenched with water and aqueous phase was extracted with MTBE (3 times). The combined organic phases were dried with $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel using heptane/ethyl acetate (10 to 7:3) to give **27** as a white amorphous solid (75 mg, 0.2 mmol, 58 %). Compound **27**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.82 (d, J = 8.1 Hz, 1 H), 7.50 (d, J = 7.4 Hz, 2 H), 7.40 (t, J = 7.4 Hz, 2 H), 7.33 (t, J = 7.4 Hz, 1 H), 7.20 (d, J = 1.7 Hz, 1 H), 7.15 (d, J = 8.1 Hz, 1 H), 6.95 (s, 1 H), 5.21 (s, 2 H), 3.88 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.3, 158.4, 141.3, 137.7, 136.5, 132.3, 128.9 (2 C), 128.3, 127.2 (2 C), 121.7, 118.9, 112.6, 107.7, 71.1, 52.5 ppm. IR: $\tilde{\nu}$ = 3082, 2948, 1697, 1602, 1406, 1256, 1028, 721 cm^{-1}. HRMS (ESI) m/z calcd. for $C_{17}H_{15}BrClO_3$ $[M + H]^+$ 380.9888, found 380.9894.

General Procedure for the Synthesis of trienes 23–25, 28, 29, 32: To a solution of (*Z*)-1-bromo-2-chloro-alkene **20**, **21**, **26**, **27**, **31** and (*E*)-4,4,5,5-tetramethyl-2-(3-methylbuta-1,3-dien-1-yl)-1,3,2-dioxaborolane[12] (3.0 equiv.) in THF/water, 2:1 were added tetrakis(triphenylphosphine) palladium(0) (5 mol-%) and K_3PO_4 (4.0 equiv.). The mixture was stirred, in the dark, for 8 h at 50 °C then cooled to room temperature. A saturated solution of NH_4Cl was added to the crude mixture. The aqueous layer was then extracted with MTBE (three times) and the combined organic phases were dried with $MgSO_4$, filtered and concentrated under reduced pressure. The crude mixture was purified by column chromatography on silica gel using a gradient of heptane and ethyl acetate. Same procedure for compound **22**, replacing H_3PO_4 by Cs_2CO_3, in THF.

Methyl 4-[(1Z,3E)-1-Chloro-5-methylhexa-1,3,5-trien-1-yl]-3-methoxybenzoate (23): Starting from compound **20** (66 mg, 0.22 mmol), compound **23** was obtained as a light yellow oil (24 mg, 0.08 mmol, 36 %). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.64 (dd, J = 8.0, 1.5 Hz, 1 H), 7.58 (d, J = 1.5 Hz, 1 H), 7.58 (d, J = 8.0 Hz, 1 H), 6.90 (d, J = 10.2 Hz, 1 H), 6.74 (dd, J = 15.3, 10.2 Hz, 1 H), 6.53 (d, J = 15.3 Hz, 1 H), 5.10 (s, 2 H), 3.92 (s, 6 H), 1.96 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.8, 156.8, 142.6, 139.6, 132.2, 131.7, 131.2, 130.5, 127.9, 125.3, 122.1, 119.2, 112.4, 56.3, 52.6, 18.7 ppm. HRMS (ESI) m/z calcd. for $C_{16}H_{18}ClO_3$ $[M + H]^+$ 293.0939, found 293.0959.

Methyl 4-[(1Z, 3E)-1-Chloro-5-methylhexa-1,3,5-trien-1-yl]-2-hydroxybenzoate (24): From compound **21** (100 mg, 0.35 mmol) compound **24** was obtained as a light yellow oil (370 mg, 0.13 mmol, 38 %). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 10.76 (s, 1 H), 7.80 (d, J = 8.5 Hz, 1 H), 7.28 (d, J = 1.9 Hz, 1 H), 7.17 (dd, J = 8.5, 1.9 Hz, 1 H), 6.94 (d, J = 9.7 Hz, 1 H), 6.73 (dd, J = 15.2, 9.7 Hz, 1 H), 6.61 (d, J = 15.2 Hz, 1 H), 5.15 (s, 2 H), 3.95 (s, 3 H), 1.96 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.4, 161.7, 144.8, 142.4, 140.8, 131.3, 130.1, 128.6, 125.2, 120.1, 117.1, 115.4, 112.3, 52.7, 18.7 ppm. HRMS (ESI) m/z calcd. for $C_{15}H_{16}ClO_3$ $[M + H]^+$ 279.0782, found 279.0788.

Methyl 5-[(1Z,3E)-1-Chloro-5-methylhexa-1,3,5-trien-1-yl]picolinate (25): From compound **22** (114 mg, 0.41 mmol), compound **25** was obtained as a light yellow oil (70 mg, 0.26 mmol, 65 %). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.98 (d, J = 1.9 Hz, 1 H), 8.13 (d, J = 8.3 Hz, 1 H), 8.07 (dd, J = 8.3, 2.0 Hz, 1 H), 6.99 (d, J = 9.0 Hz, 1 H), 6.73 (dd, J = 15.5, 9.0 Hz, 1 H), 6.68 (d, J = 15.5 Hz), 5.19 (s, 2 H), 4.00 (s, 3 H), 1.97 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.5, 147.4, 147.1, 142.2, 141.8, 137.6, 136.9, 134.6, 129.7, 125.1, 124.6, 120.8, 53.3, 18.6 ppm. HRMS (ESI) m/z calcd. for $C_{14}H_{15}ClNO_2$ $[M + H]^+$ 264.0786, found 264.0801.

Methyl 4-[(1Z,3E)-1-Chloro-5-methylhexa-1,3,5-trien-1-yl]-2-methoxybenzoate (28): From compound **26** (200 mg, 0.65 mmol) compound **28** was obtained as a light yellow oil (110 mg, 0.38 mmol, 64 %). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.80 (d, J = 8.5 Hz, 1 H), 7.25 (d, J = 1.7 Hz, 1 H), 7.25 (dd, J = 8.6, 1.7 Hz, 1 H), 6.91 (d, J = 9.7 Hz, 1 H), 6.71 (dd, J = 15.3, 9.7 Hz, 1 H), 6.6 (d, J = 15.3 Hz, 1 H), 5.14 (s, 2 H), 3.95 (s, 3 H), 3.89 (s, 3 H), 1.95 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.4, 159.5, 143.0, 142.4, 140.5, 132.1, 131.5, 128.1, 125.1, 119.9, 119.8, 118.0, 110.3, 56.4, 52.4, 18.7 ppm. HRMS (ESI) m/z calcd. for $C_{16}H_{18}ClO_3$ $[M + H]^+$ 293.0939, found 293.0959.

Methyl 2-(Benzyloxy)-4-[(1Z,3E)-1-chloro-5-methylhexa-1,3,5-trien-1-yl]benzoate (29): From compound **27** (106 mg, 0.29 mmol) compound **29** was obtained as a light yellow oil (91 mg, 0.25 mmol, 86 %). As this compound was unstable (a correct ^{13}C NMR spectrum could never be obtain), it was immediately engaged in the next step after purification. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.83 (d, J = 8.3 Hz, 1 H), 7.52 (m, 2 H, 18-H), 7.40 (m, 2 H), 7.33 (m, 1 H), 7.30 (m, 2 H), 6.86 (d, J = 10.3 Hz, 1 H), 6.72 (dd, J = 15.4, 10.4 Hz, 1 H), 6.59 (d, J = 15.3 Hz, 1 H), 5.23 (s, 2 H), 5.15 (s, 2 H), 3.90 (s, 3 H), 2.04 (s, 3 H) ppm. HRMS (ESI) m/z calcd. for $C_{22}H_{22}ClO_3$ $[M + H]^+$ 369.1252, found 369.1261.

4-[(1Z,3E)-1-Chloro-5-methylhexa-1,3,5-trien-1-yl]benzyl Acetate (32): Starting from compound **31** (500 mg, 1.73 mmol), compound **32** was obtained as a light yellow oil (312 mg, 1.13 mmol, 66 %). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.64 (d, J = 8.5 Hz, 2 H), 7.35 (d, J = 8.5 Hz, 2 H), 6.83 (d, J = 9.6 Hz, 1 H), 6.73 (dd, J = 15.4, 9.6 Hz, 1 H), 6.57 (d, J = 15.4 Hz, 1 H), 5.12 (s, 2 H), 5.11 (s, 2 H), 2.11 (s, 3 H), 1.97 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.1, 142.5, 139.3, 138.0, 136.6, 132.4, 128.5, 126.7, 126.5, 125.4, 119.1, 66.0, 21.2, 18.7 ppm. HRMS (ESI) m/z calcd. for $C_{16}H_{18}ClO_2$ $[M + H]^+$ 277.0990, found 277.1006.

General Procedure for the Diels–Alder Reactions: A solution of triene (1.2 equiv.), dienophile **3b** or **8** (1 equiv.) and 2-bromophenylboronic acid (30 mol-%) in dichloromethane was heated at reflux for 2 d. The reaction mixture was then concentrated under reduced pressure and purified by column chromatography on silica gel using heptane/ethyl acetate (10 to 8:2) + 0.1 % Acetic acid to give the decalins **34**–**44**.

(2R,4aR,5S,8aR)-5-{(Z)-2-[4-(Acetoxymethyl)phenyl]-2-chlorovinyl}-7-methyl-2-[(R)-6-methylhept-5-en-2-yl]-1,5,8,8a-tetrahydronaphthalene-4a(2H)-carboxylic Acid (34): Compound **34** (200 mg, 0.39 mmol, 87 %) was obtained from triene **32** (150 mg, 0.54 mmol) and dienophile 3b (106 mg, 0.45 mmol), as a pale yellow oil. Compound 34: $[\alpha]_D^{20}$ = –189.0 (c = 0.1, $CDCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.42 (d, J = 8.5 Hz, 2 H), 7.23 (d, J = 8.5 Hz, 2 H), 5.93 (d, J = 9.6 Hz, 1 H), 5.68 (dd, J = 10.2, 2.1 Hz, 1 H), 5.63 (d, J = 7.4 Hz, 1 H), 5.27 (d, J = 4.7 Hz, 1 H), 5.06 (m, 1 H), 5.04 (s, 2 H), 3.63 (dd, J = 9.1, 5.2 Hz, 1 H), 2.57 (m, 1 H), 2.29 (m, 1 H), 2.08 (s, 3 H), 1.90 (m, 4 H), 1.76 (m, 1 H), 1.67 (s, 3 H), 1.63 (s, 3 H), 1.58 (s, 3 H), 1.40 (m, 1 H), 1.27 (m, 3 H), 0.75 (d, J = 6.7 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 178.3, 171.1, 138.5, 136.4, 135.6, 134.5, 132.7, 132.4, 131.6, 129.9, 129.3, 128.4 (2 C), 127.5, 127.1 (2 C), 125.0, 117.8, 66.1, 48.3, 45.0, 37.1, 36.8, 34.1, 32.0, 29.2, 28.1, 26.3, 26.0, 23.6, 21.3, 18.0, 16.4 ppm. HRMS (ESI) m/z calcd. for $C_{31}H_{38}ClO_4$ $[M - H]^-$ 510.0910, found 510.0917.

(2R,4aR,5S,8aR)-5-[(E)-2-(4-Carboxyphenyl)prop-1-en-1-yl]-7-methyl-2-[(R)-6-methylhept-5-en-2-yl]-1,5,8,8a-tetrahydronaphthalene-4a(2H)-carboxylic Acid (35): Compound **35** (200 mg, 0.39 mmol, 87 %) was obtained from triene **12** (18 mg, 0.07 mmol) and dienophile **3b** (15 mg, 0.06 mmol), as a pale yellow

oil. Compound **35**: $[\alpha]_D^{20}$ = –188.0 (*c* = 0.1, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 8.07 (d, *J* = 8.6 Hz, 2 H), 7.73 (d, *J* = 8.6 Hz, 2 H), 6.32 (d, *J* = 9.8 Hz, 1 H), 5.70 (m, 1 H), 5.65 (m, 1 H), 5.33 (d, *J* = 4.9 Hz, 1 H), 5.14 (t, *J* = 7.5 Hz, 1 H), 3.74–3.71 (m, 1 H), 2.75–2.72 (m, 1 H), 2.45–2.40 (m, 1 H), 2.04–1.96 (m, 4 H), 1.70 (s, 3 H), 1.69 (s, 3 H), 1.63 (s, 3 H), 1.47–1.40 (m, 1 H), 1.33 (m, 3 H), 1.23 (m, 1 H), 0.89 (d, *J* = 6.7 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, MeOD): δ = 176.4, 167.8, 140.9, 137.5, 134.6, 132.3, 132.3, 132.1, 131.4, 131.3 (2 C), 128.0, 128.0 (2 C), 126.4, 118.5, 49.1, 46.7, 38.3, 38.2, 35.1, 33.1, 30.8, 30.6, 28.9, 27.5, 26.6, 26.5, 24.2 ppm. HRMS (ESI) *m/z* calcd. for $C_{29}H_{34}ClO_4$ [M – H]- 481.2151, found 481.2157.

(2*R*,4a*R*,5*S*,8a*R*)-5-{(*Z*)-2-Chloro-2-[4-(methoxycarbonyl)-phenyl]vinyl}-7-methyl-2-[(*R*)-6-methylhept-5-en-2-yl]-1,5,8,8a-tetra-hydronaphthalene-4a(2*H*)-carboxylic Acid (36): Compound **36** (750 mg, 1.50 mmol, 73 %) was obtained from triene **33** (660 mg, 2.51 mmol) and dienophile **3b** (490 mg, 2.09 mmol), as a pale yellow oil. Compound **36** $[\alpha]_D^{20}$ = –222.0 (*c* = 0.1, $CDCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.83 (d, *J* = 8.6 Hz, 2 H), 7.40 (d, *J* = 8.6 Hz, 2 H), 5.97 (d, *J* = 9.8 Hz, 1 H), 5.62 (dd, *J* = 10.0, 2.5 Hz, 1 H), 5.55 (d, *J* = 8.2 Hz, 1 H), 5.19 (d, *J* = 3.8 Hz, 1 H), 4.99 (t, *J* = 6.9 Hz, 1 H), 3.84 (s, 3 H), 3.57 (dd, *J* = 9.3, 5.1 Hz, 1 H), 2.51 (m, 1 H), 2.22 (m, 1 H), 1.84 (m, 4 H), 1.68 (m, 1 H), 1.60 (s, 3 H), 1.57 (s, 3 H), 1.52 (s, 3 H), 1.47 (m, 1 H), 1.30 (m, 3 H), 0.66 (d, *J* = 6.6 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 179.8, 166.9, 142.6, 136.0, 134.6, 132.6, 131.9, 131.6, 130.0, 129.8, 129.2, 126.8 (2 C), 125.0, 117.4, 52.5, 48.4, 45.0, 37.0, 36.8, 34.2, 32.0, 29.1, 28.1, 26.3, 26.0, 23.6, 18.0, 16.3 ppm. HRMS (ESI) *m/z* calcd. for $C_{30}H_{36}ClO_4$ $[M – H]^-$ 495.2302, found 495.2339.

(2*R*,4a*R*,5*S*,8a*R*)-5-{(*Z*)-2-Chloro-2-[3-hydroxy-4-(methoxy-carbonyl)phenyl]vinyl}-7-methyl-2-[(*R*)-6-methylhept-5-en-2-yl]-1,5,8,8a-tetrahydronaphthalene-4a(2*H*)-carboxylic Acid (37): Compound **37** (18 mg, 0.035 mmol, 59 %) was obtained from triene **24** (21 mg, 0.08 mmol) and dienophile **3b** (15 mg, 0.06 mmol) as a pale yellow oil. Compound **37** $[\alpha]_D^{20}$ = –236.0 (*c* = 0.1, $CDCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 10.6 (s, 1 H), 7.68 (d, *J* = 8.3 Hz, 1 H), 7.10 (d, *J* = 1.7 Hz, 1 H), 6.95 (d, *J* = 8.4, 1.7 Hz, 1 H), 6.07 (d, *J* = 9.6 Hz, 1 H), 5.70 (dd, *J* = 10.1, 2.3 Hz, 1 H), 5.64 (d, *J* = 5.5 Hz, 1 H), 5.26 (d, *J* = 4.4 Hz, 1 H), 5.07 (t, *J* = 6.6 Hz, 1 H), 3.94 (s, 3 H), 3.65 (dd, *J* = 9.1, 5.5 Hz, 1 H), 2.59 (m, 1 H), 2.30 (m, 1 H), 1.93 (m, 4 H), 1.79 (m, 1 H), 1.67 (s, 3 H), 1.64 (s, 3 H), 1.59 (s, 3 H), 1.49 (m, 1 H), 1.37 (m, 3 H), 0.77 (d, *J* = 6.6 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 178.9, 170.4, 161.6, 145.3, 136.1, 132.8, 131.6, 130.0, 129.8, 129.6, 125.0, 117.6, 117.3, 115.9, 112.2, 52.6, 48.2, 45.1, 37.0, 36.8, 34.2, 32.0, 29.1, 28.1, 26.3, 26.0, 23.6, 18.0, 16.3 ppm. HRMS (ESI) *m/z* calcd. for $C_{30}H_{36}ClO_5$ $[M – H]^-$ 511.2251, found 511.2295.

(2*R*,4a*R*,5*S*,8a*R*)-5-{(*Z*)-2-Chloro-2-[3-methoxy-4-(methoxy-carbonyl)phenyl]vinyl}-7-methyl-2-[(*R*)-6-methylhept-5-en-2-yl]-1,5,8,8a-tetrahydronaphthalene-4a(2*H*)-carboxylic Acid (38): Compound **38** (70 mg, 0.13 mmol, 47 %) was obtained from triene **28** (100 mg, 0.34 mmol) and dienophile **3b** (67 mg, 0.28 mmol) as a pale yellow oil. Compound **38**: $[\alpha]_D^{20}$ = –209.0 (*c* = 0.1, $CDCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.68 (d, *J* = 8.6 Hz, 1 H), 7.03 (d, *J* = 1.7 Hz), 6.98 (dd, *J* = 8.5, 1.7 Hz), 6.01 (d, *J* = 9.6 Hz, 1 H), 5.67 (dd, *J* = 10.1, 2.4 Hz, 1 H), 5.6 (d, *J* = 8.1 Hz, 1 H), 5.25 (d, *J* = 4.0 Hz, 1 H), 5.05 (t, *J* = 6.9 Hz, 1 H), 3.88 (s, 3 H), 3.86 (s, 3 H), 3.6 (dd, *J* = 10.1, 3.1 Hz, 1 H), 2.56 (m, 1 H), 2.29 (m, 1 H), 1.90 (m, 4 H, 4-H), 1.75 (m, 1 H), 1.67 (s, 3 H), 1.63 (s, 3 H), 1.58 (s, 3 H), 1.51 (m, 1 H), 1.29 (m, 3 H), 0.71 (d, *J* = 6.7 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 180.3, 166.4, 159.3, 143.5, 135.9, 132.5, 132.0, 131.7, 131.5, 129.8, 129.2, 125.0, 119.6, 118.5, 117.3, 110.6, 56.2, 52.3, 48.4, 44.9, 37.0, 36.7, 34.2, 31.9, 29.1, 28.1, 26.2, 26.0, 23.6, 17.9, 16.2 ppm. HRMS (ESI) *m/z* calcd. for $C_{31}H_{38}ClO_5$ $[M – H]^-$ 525.2408, found 525.2381.

(2*R*,4a*R*,5*S*,8a*R*)-5-{(*Z*)-2-Chloro-2-[6-(methoxycarbonyl)pyridin-3-yl]vinyl}-7-methyl-2-[(*R*)-6-methylhept-5-en-2-yl]-1,5,8,8a-tetrahydronaphthalene-4a(2*H*)-carboxylic Acid (39): Compound **39** (13.8 mg, 0.023 mmol, 14 %) was obtained from triene **29** (75 mg, 0.20 mmol) and dienophile **3b** (40 mg, 0.17 mmol) as a pale yellow oil. Compound **39**: $[\alpha]_D^{20}$ = –210.0 (*c* = 0.1, $CDCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.65 (d, *J* = 8.1 Hz, 1 H), 7.45 (m, 2 H), 7.30 (m, 2 H), 7.24 (m, 1 H), 6.99 (d, *J* = 1.7 Hz, 1 H), 6.95 (dd, *J* = 8.1, 1.8 Hz, 1 H), 5.87 (d, *J* = 9.8 Hz, 1 H), 5.61 (dd, *J* = 10.0, 2.4 Hz, 1 H), 5.53 (d, *J* = 8.3 Hz, 1 H), 5.17 (d, *J* = 4.1 Hz, 1 H), 5.09 (s, 2 H), 4.99 (t, *J* = 6.9 Hz, 1 H), 3.80 (s, 3 H), 3.54 (m, 1 H), 2.49 (m, 1 H), 2.24 (m, 1 H), 1.83 (m, 4 H), 1.71 (m, 1 H), 1.60 (s, 3 H), 1.56 (s, 3 H), 1.52 (s, 3 H), 1.44 (m, 1 H), 1.29 (m, 3 H), 0.67 (d, *J* = 6.6 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 179.5, 166.6, 158.3, 143.4, 137.0, 136.0, 132.7, 132.1, 131.7, 131.6, 129.7, 129.1, 128.8 (2 C), 128.1, 127.3 (2 C), 125.0, 120.4, 118.9, 117.3, 112.5, 70.9, 52.3, 48.3, 44.9, 37.0, 36.8, 34.2, 31.9, 29.1, 28.1, 26.3, 26.0, 23.6, 18.0, 16.3 ppm. HRMS (ESI) *m/z* calcd. for $C_{37}H_{42}ClO_5$ $[M – H]^-$ 601.2721, found 601.2762.

(2R,4aR,5S,8aR)-5-{(*Z*)-2-Chloro-2-[6-(methoxycarbonyl)pyridin-3-yl]vinyl}-7-methyl-2-[(*R*)-6-methylhept-5-en-2-yl]-1,5,8,8a-tetrahydronaphthalene-4a(2*H*)-carboxylic Acid (41): Compound **41** (51 mg, 0.10 mmol, 60 %) was obtained from triene **25** (54 mg, 0.20 mmol) and dienophile **3b** (40 mg, 0.17 mmol) a pale yellow oil. Compound **41**: $[\alpha]_D^{20}$ = –161.0 (*c* = 0.1, $CDCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 8.83 (d, *J* = 2.3 Hz, 1 H), 7.99 (d, *J* = 8.2 Hz, 1 H), 7.84 (dd, *J* = 8.2, 2.3 Hz, 1 H), 6.20 (d, *J* = 9.5 Hz, 1 H), 5.65 (m, 2 H), 5.24 (d, *J* = 3.9 Hz, 1 H), 5.05 (t, *J* = 7.0 Hz, 1 H), 3.95 (s, 3 H), 3.68 (dd, *J* = 9.5, 3.9 Hz, 1 H), 2.62 (m, 1 H), 2.30 (m, 1 H), 1.93 (m, 4 H), 1.79 (m, 1 H), 1.66 (s, 3 H), 1.65 (s, 3 H), 1.57 (s, 3 H), 1.41 (m, 1 H), 1.12 (m, 3 H), 0.78 (d, *J* = 6.6 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 178.3, 165.2, 147.3, 137.3, 136.7, 135.2, 132.5, 131.8, 131.5, 130.1, 128.2, 125.0, 124.8, 116.9, 53.1, 48.3, 45.3, 37.0, 36.8, 36.6, 34.1, 31.9, 29.1, 28.1, 26.3, 26.0, 23.6, 17.9, 16.4 ppm. HRMS (ESI) *m/z* calcd. for $C_{29}H_{35}ClNO_4$ $[M – H]^-$ 496.2255, found 496.2264.

(2R,4aS,5S,8aR)-5-{(*Z*)-2-Chloro-2-[4-(methoxycarbonyl)-phenyl]vinyl}-2-{2-[(4-chlorobenzoyl)oxy]ethyl}-7-methyl-1,3,4,5,8,8a-hexahydronaphthalene-4a(2*H*)-carboxylic Acid (42): Compound **42** (763 mg, 1.34 mmol, 96 %) was obtained from triene **28** (549 mg, 2.08 mmol) and dienophile **8** (140 mg, 0.70 mmol) as a pale yellow amorphous solid. Compound **42**: $[\alpha]_D^{20}$ = –97.50 (*c* = 0.5, MeOH). ^1H NMR (500 MHz, $[D_6]$acetone): δ = 13.00–9.00 (br. s, 2 H), 8.04 (d, *J* = 8.5 Hz, 2 H), 8.00 (d, *J* = 8.5 Hz, 2 H), 7.70 (d, *J* = 8.4 Hz, 2 H), 7.56 (d, *J* = 8.4 Hz, 2 H), 6.33 (d, *J* = 9.5 Hz, 1 H), 5.77 (dd, *J* = 10.2, 2.7 Hz, 1 H), 5.70 (d, *J* = 10.2 Hz, 1 H), 5.30–5.27 (m, 1 H), 4.44–4.38 (m, 2 H), 3.89 (s, 3 H), 3.75–3.69 (m, 1 H), 2.76–2.69 (m, 1 H), 2.63–2.56 (m, 1 H), 2.10 (dd, *J* = 18.1, 8.9 Hz, 1 H), 1.95–1.83 (m, 4 H), 1.78–1.70 (m, 1 H), 1.65 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $[D_6]$acetone): δ = 175.6, 166.7, 165.9, 143.0, 139.6, 136.5, 133.1, 132.0 (2 C), 131.6, 131.5, 131.1, 130.8, 130.3 (2 C), 130.2, 129.7 (2 C), 127.3 (2 C), 117.9, 63.8, 52.5, 48.6, 45.8, 35.7, 32.4, 31.6, 30.0, 30.1, 23.5 ppm. HRMS (ESI): *m/z* calcd. for $C_{31}H_{29}Cl_2O_6^-$ $[M – H]^-$ 567.1341, found 567.1389.

(2*R*,4a*R*,5*S*,8a*R*)-5-{(*Z*)-2-Chloro-2-[3-methoxy-4-(methoxy-carbonyl)phenyl]vinyl}-2-{2-[(4-chlorobenzoyl)oxy]ethyl}-7-methyl-1,5,8,8a-tetrahydronaphthalene-4a(2*H*)-carboxylic Acid (43): Compound **43** (18 mg, 0.030 mmol, 37 %) was obtained from triene **28** (27 mg, 0.09 mmol) and dienophile **8** (24 mg, 0.08 mmol) as a pale yellow oil. Compound **43**: $[\alpha]_D^{20}$ = –64.0 (*c* = 0.1, $CDCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.95 (d, *J* = 8.6 Hz, 2 H), 7.71 (dd, *J* = 8.2 Hz, 1 H), 7.41 (d, *J* = 8.6 Hz, 2 H), 7.05 (m, 2 H), 6.07 (d, *J* = 9.8 Hz, 1 H), 5.73 (td, *J* = 9.8, 2.7 Hz, 1 H), 5.65 (d, *J* = 9.8 Hz, 1 H),

5.25 (d, J = 3.7 Hz, 1 H), 4.35 (td, J = 6.4, 2.1 Hz, 2 H), 3.89 (s, 3 H), 3.87 (s, 3 H), 3.66 (m, 1 H), 2.59 (m, 1 H), 2.48 (m, 1 H), 2.04 (dd, J = 18.1, 7.4 Hz, 1 H), 1.84 (m, 4 H), 1.64 (s, 3 H), 1.25 (s, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 206.7, 179.3, 166.4, 166.0, 159.4, 143.4, 139.7, 135.6, 133.2, 133.1, 132.0, 131.3 (2 C), 129.5, 129.4, 129.0 (2 C), 119.7, 118.6, 118.5, 117.5, 110.7, 63.3, 56.3, 52.4, 44.7, 34.9, 32.1, 31.1, 29.5, 29.0, 23.6 ppm. HRMS (ESI) m/z calcd. for $C_{32}H_{31}Cl_2O_7$ [M – H]$^-$ 597.1447, found 597.1461.

(2*R*,4a*R*,5*S*,8a*R*)-5-{(*Z*)-2-Chloro-2-[2-methoxy-4-(methoxycarbonyl)phenyl]vinyl}-2-{2-[(4-chlorobenzoyl)oxy]ethyl}-7-methyl-1,5,8,8a-tetrahydronaphthalene-4a(2*H*)-carboxylic Acid (44): Compound **44** (23 mg, 0.038 mmol, 55 %) was obtained from triene **23** (24 mg, 0.08 mmol) and dienophile **8** (21 mg, 0.07 mmol) as a pale yellow oil. Compound **44**: $[\alpha]_D^{20}$ = –62.0 (c = 0.1, $CDCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.92 (d, J = 8.4 Hz, 2 H), 7.50 (dd, J = 8.0, 1.4 Hz, 1 H), 7.45 (dd, J = 11.8, 1.4 Hz, 1 H), 7.37 (d, J = 8.4 Hz, 2 H), 7.32 (d, J = 8.0 Hz, 1 H), 5.72 (d, J = 9.7 Hz, 1 H), 5.47–5.39 (m, 2 H), 5.00–4.99 (m, 1 H), 4.06–4.01 (m, 2 H), 3.60 (s, 3 H), 3.51 (s, 3 H), 3.43–3.38 (m, 1 H), 2.26–2.22 (m, 1 H), 2.19–2.13 (m, 1 H), 1.75 (m, 1 H), 1.55–1.36 (m, 4 H), 1.34 (s, 3 H), 0.95 (m, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 179.5, 177.8, 166.8, 166.0, 156.7, 139.6, 138.0, 135.1, 133.0, 132.3, 131.8, 131.2 (2 C), 130.5, 129.9, 129.0 (2 C), 128.2, 121.8, 118.0, 112.2, 63.4, 56.1, 52.6, 48.4, 44.7, 35.0, 32.2, 31.2, 29.4, 28.9, 23.6 ppm. HRMS (ESI) m/z calcd. for $C_{32}H_{31}Cl_2O_7$ [M – H]$^-$ 597.1447, found 597.1440.

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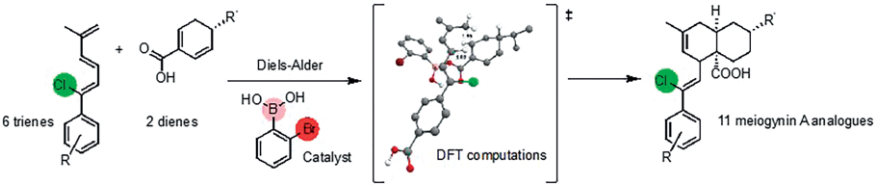

Eleven analogs of the natural product meiogynin A, an inhibitor of proteins of the Bcl-2 family, have been elaborated by an intermolecular Diels–Alder (DA) reaction of various conjugated chloro-trienes with two α,β-unsaturated carboxylic acids as dienophiles. The perfect regioselectivity and good to excellent diastereoselectivities of these reactions were rationalized by DFT calculations.

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