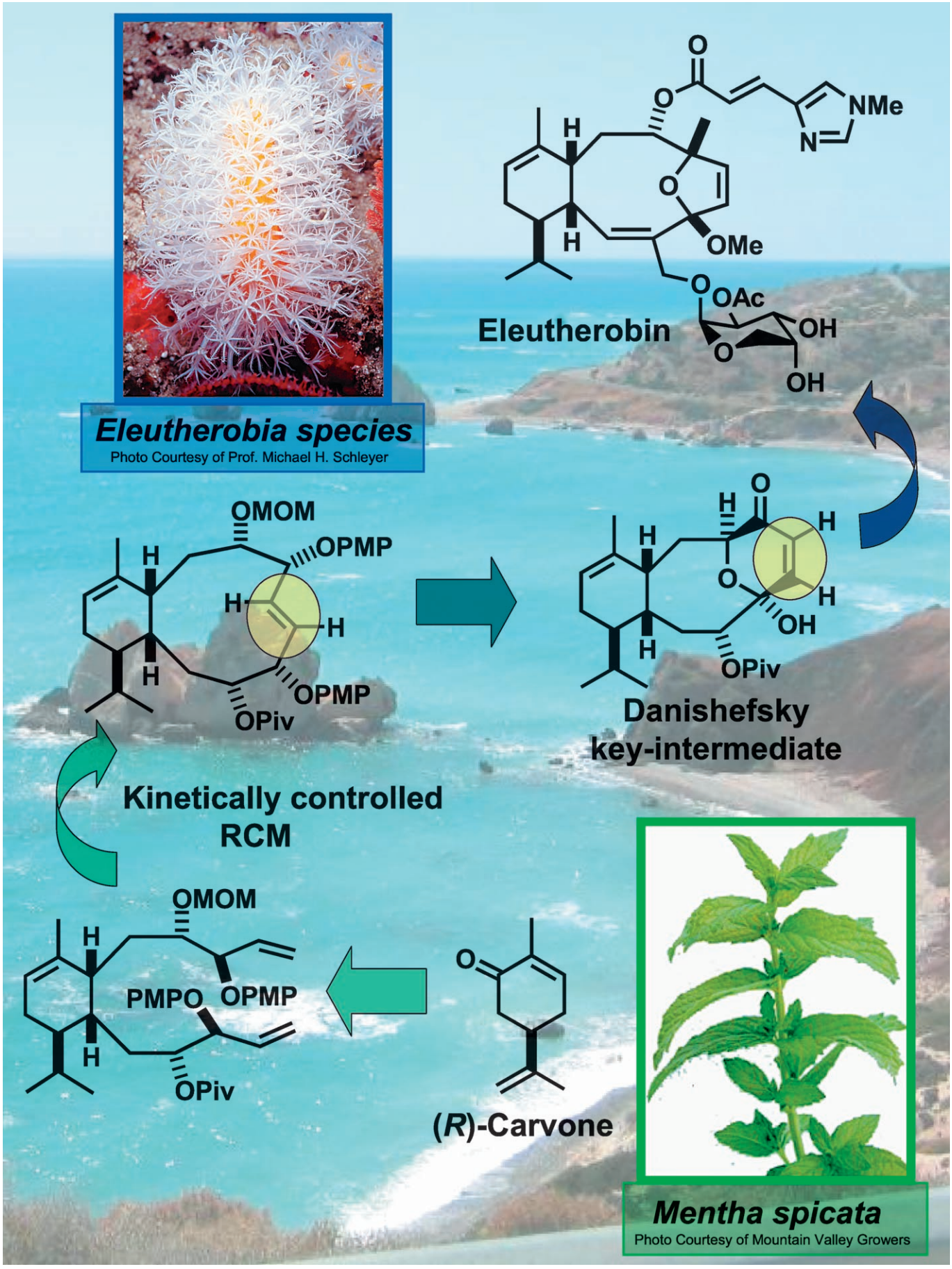


CHEMISTRY
A EUROPEAN JOURNAL

DOI: 10.1002/chem.200500749

A Formal Total Synthesis of Eleutherobin Using the Ring-Closing Metathesis (RCM) Reaction of a Densely Functionalized Diene as the Key Step: Investigation of the Unusual Kinetically Controlled RCM Stereochemistry

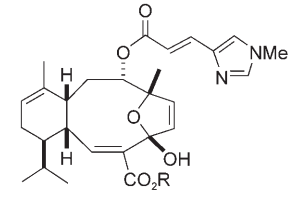
Damiano Castoldi,[a] Lorenzo Caggiano,[a, c] Laura Panigada,[a] Ofer Sharon,[a] Anna M. Costa,[b] and Cesare Gennari*[a]

Abstract: Asymmetric oxyallylation reactions and ring-closing metathesis have been used to synthesize compound **3**, a key advanced intermediate used in the total synthesis of eleutherobin reported by Danishefsky and co-workers. The aldehyde **6**, which is readily prepared from commercially available *R*-(−)-carvone in six steps in 30% overall yield on multigram quantities, was converted into the diene **5** utilizing two stereoselective titanium-mediated Hafner–Duthaler oxyallylation reactions. The reactions gave the desired products (**8** and **12**) in high yields (73 and 83%, respectively) as single diastereoisomers, with the allylic alcohol already protected as the *p*-methoxyphenyl (PMP) ether, which previous work has demonstrated actually aids ring-closing metathesis compared to other protective groups and the corresponding free alcohol. Cyclization under forcing conditions, using Grubbs' second-generation catalyst **13**, gave the ten-membered carbocycle (*E*)-**14** in 64% yield. This result is in sharp contrast to similar, but less functionalized, dienes, which have all undergone cyclization to give the *Z* stereoisomers exclusively. A detailed investigation of this unusual cyclization stereochemistry by computational methods has shown that the *E* isomer of the ten-membered carbocycle is indeed less thermodynamically stable than the corresponding *Z* isomer. In fact, the selectivity is believed to be due to the dense functionality around the ruthenacyclobutane intermediate that favors the *trans*-ruthenacycle, which ultimately leads to the less stable *E* isomer of the ten-membered carbocycle under kinetic control. During the final synthetic manipulations the double bond of enedione (*E*)-**16** isomerized to the more thermodynamically stable enedione (*Z*)-**4**, giving access to the advanced key-intermediate **3**, which was spectroscopically and analytically identical to the data reported by Danishefsky and co-workers, and thereby completing the formal synthesis of eleutherobin.

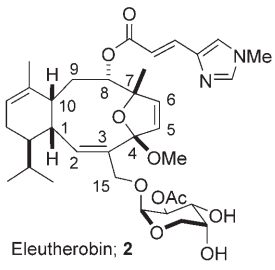
Keywords: antitumor agents · natural products · ring-closing metathesis · stereocontrol · total synthesis

Introduction

Sarcodictyins A (**1a**) and B (**1b**) were isolated in 1987 by Pietra and co-workers from the Mediterranean stoloniferan coral *Sarcodictyon roseum*.[1] Their antitumor activity and



R = Me: Sarcodictyin A; **1a**
R = Et: Sarcodictyin B; **1b**



Eleutherobin; **2**

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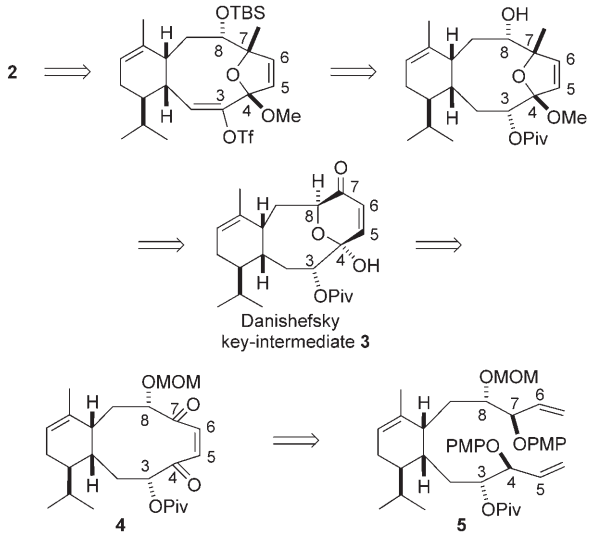
paclitaxel-like mechanism of action were recognized about a decade later (1996).[2] In the meantime, the diterpene glycoside eleutherobin (**2**) was reported by Fenical et al. from an *Eleutherobia* species of Australian soft coral, accompanied by disclosure of its potent cytotoxicity (1995).[3] Two years later, eleutherobin was shown to act similarly to sarcodictyins, effecting mitotic arrest through tubulin polymerization.[4] Both sarcodictyins and eleutherobin (the "eleutheside" family of microtubule-stabilizing drugs) are characterized by an activity profile different from that of paclitaxel; in particular, they are active against paclitaxel-resistant tumor cell lines and therefore have potential as second-generation microtubule-stabilizing anticancer agents.[4,5] The scarce availability of **1** and **2** from natural sources makes their total syntheses vital for further biological investigations.[5] To date, sarcodictyins A and B have been synthesized successfully by Nicolaou et al.,[6] who have also exploited a similar route to eleutherobin.[7] A subsequent report by Danishefsky and co-workers details an elegant alternative access to eleutherobin.[8] A number of synthetic approaches to the eleutheside natural products and syntheses of simplified analogues have also been described.[9]

Herein we report the preparation of **3**, a key intermediate in the synthesis reported by Danishefsky and co-workers,[8] and thus a formal total synthesis of eleutherobin (**2**) (Scheme 1).[10]

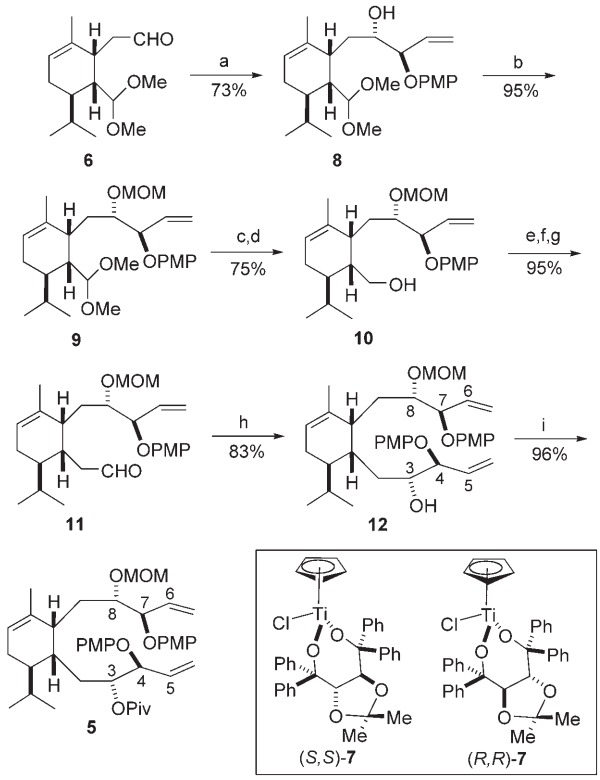


Scheme 1. Retrosynthetic analysis of eleutherobin (**2**).

The key step of our strategy, used for obtaining the [8.4.0]-fused bicyclic ring system **4**, is a ring-closing metathesis (RCM)[11] reaction of the densely functionalized diene **5**. The unusual kinetically controlled RCM stereochemical outcome has been investigated using computational methods.

Results and Discussion

Synthesis of the key-intermediate 3: Diene **5** was synthesized from aldehyde **6** (prepared in six steps on a multigram scale from *R*-(−)-carvone in 30% overall yield)[9a,g] incorporating two stereoselective Hafner–Duthaler oxyallylation reactions[12] (Scheme 2). The first oxyallylation, in the presence of the [TiCl(Cp){(*S*,*S*)-Taddol}] complex **7**, proceeded with complete stereocontrol to give the desired stereoisomer **8** in 73% isolated yield. After standard protection of the alcohol as methoxymethyl ether **9** in 95% yield, cleavage of the dimethylacetal group and reduction with $NaBH_4$ to give **10** in 75% yield, an efficient and well-established sequence of steps[8c,9n] led to the homologated aldehyde **11** (95%).[9q] The same oxyallylation procedure described above was again applied, this time using the [TiCl(Cp){(*R*,*R*)-Taddol}] complex **7**, to give the desired alcohol **12** in 83% yield with

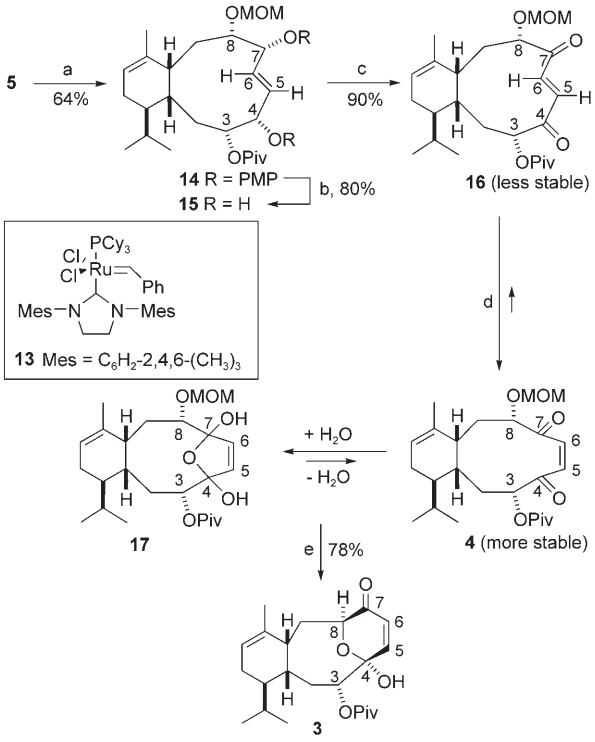


Scheme 2. Reagents and conditions: a) *sec*-BuLi (1.3 M in cyclohexane), PMPOAllyl, [TiCl(Cp){(*S*,*S*)-Taddol}] (**7**), THF/Et_2O (57:43), −78 °C→0 °C, 73%; b) DIPEA, TBAI, MOMCl, CH_2Cl_2, 25 °C, 95%; c) $LiBF_4$, CH_3CN/H_2O (98:2), 25 °C; d) $NaBH_4$, EtOH, 25 °C, 75% over two steps; e) MsCl, TEA, CH_2Cl_2, 0 °C→25 °C, 95%; f) KCN, [18]crown-6, CH_3CN, 80 °C, quant.; g) DIBAL-H, toluene/hexane (1:2), −78 °C, quant.; h) *sec*-BuLi (1.4 M in cyclohexane), PMPOAllyl, [TiCl(Cp){(*R*,*R*)-Taddol}] (**7**), Et_2O/THF (81:19), −78 °C→25 °C, 83%; i) PivCl, DMAP, DIPEA, CH_2Cl_2, 25 °C, 96%. PMP = *p*-methoxyphenyl; DIPEA = diisopropylethylamine; TBAI = tetrabutylammonium iodide; MOMCl = chloromethyl methyl ether; MsCl = methanesulfonyl chloride; TEA = triethylamine; DIBAL-H = diisobutylaluminum hydride; Piv = *tert*-BuCO; DMAP = 4-(dimethylamino)pyridine.

complete stereocontrol. Homoallylic alcohol **12** was then transformed into the pivalate **5** (96%), and this diene was subjected to ring-closing metathesis (RCM).

The RCM reaction of a number of densely functionalized diene cyclization precursors of type **5** (bearing protected and/or free alcohol functionalities at both the allylic and the homoallylic positions) had previously been investigated with a variety of catalysts, but no desired cyclized frameworks were ever obtained.[9o] However, none of the previously examined diene precursors had the allylic alcohols protected as *p*-methoxyphenyl (PMP) ethers, which were discovered to facilitate the RCM reaction with respect to other protective groups and the corresponding free alcohols.[9o]

Based on these premises, diene **5** was treated with the second-generation Grubbs RCM catalyst[13] **13** (Scheme 3). Under forcing conditions[14] [slow addition by syringe-pump

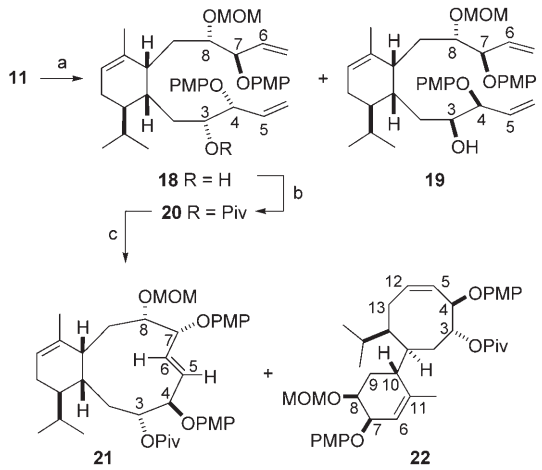


Scheme 3. Reagents and conditions: a) cat. **13** (30% mol), toluene, 110°C, 6.5 h, 64%; b) CAN, CH_3CN/H_2O (4:1), 0°C, 80%; c) DMP, CH_2Cl_2, 25°C, 90%; d) $CDCl_3$, 25°C; e) $BF_3{\cdot}Et_2O$, Me_2S, CH_2Cl_2, −78°C→−20°C, 78%. CAN = ceric ammonium nitrate; DMP = Dess–Martin periodinane.

(over 2.5 h) of a solution of RCM catalyst **13** (30% mol) in toluene to a boiling solution of **5** in toluene, and additional stirring for 4 h at 110°C], the (*E*)-**14**[15] stereoisomer was formed and isolated in 64% yield. This result contrasts sharply with many other *Z*-selective RCM reactions of diene cyclization precursors less densely functionalized than diene **5**, which possessed protected and/or free alcohol functionalities at both the homoallylic positions and at only one allylic position.[9h,m–o,q] In the presence of a second-generation Grubbs catalyst, these dienes lead to the more stable *Z*-cyclized products under thermodynamic control.[16]

Confident that the greater stability of the *Z* isomer of the ten-membered carbocycle would eventually prevail, we continued our planned synthesis by removal of the PMP groups (CAN, 80%) and oxidation of the allylic diol (DMP, 90%). Enedione **16** (H-5, H-6: $\delta = 7.07$, 6.64 ppm; $^3J_{\text{H-5/H-6}} = 17.3$ Hz) showed remarkable properties: while recording its ^{1}H NMR spectrum in $CDCl_3$ it cleanly isomerized to the more thermodynamically stable stereoisomer (*Z*)-**4** (H-5, H-6: $\delta = 7.20$, 6.13 ppm; $^3J_{\text{H-5/H-6}} = 14.0$ Hz; $t_{1/2} = 63$ h). By addition of a catalytic amount of I_2 (10 mol%) a complete isomerization was observed in a shorter time (24 h). Bis-hemiacetal **17** (H-5, H-6: $\delta = 6.29$, 6.18 ppm; $^3J_{\text{H-5/H-6}} = 5.8$ Hz) was obtained as the only product after flash chromatography of the enedione (*Z*)-**4**, showing the propensity of **4** to add a molecule of water and equilibrate with its hydrated form.[17] Finally, the MOM protective group of the **16**/**4**/**17** mixture was removed ($BF_3{\cdot}Et_2O$, Me_2S)[18] to give compound **3** (78%), which produced analytical data identical to those previously reported by Danishefsky and co-workers (^{1}H NMR, ^{13}C NMR, and IR spectroscopy, HRMS, R_f, and $[\alpha]_D$).[8c]

The RCM reaction of **20**, a diastereoisomer of diene **5**, was also investigated (Scheme 4). Aldehyde **11** was oxyallylated using the (*Z*)-oxyallylborane derived from (−)-α-



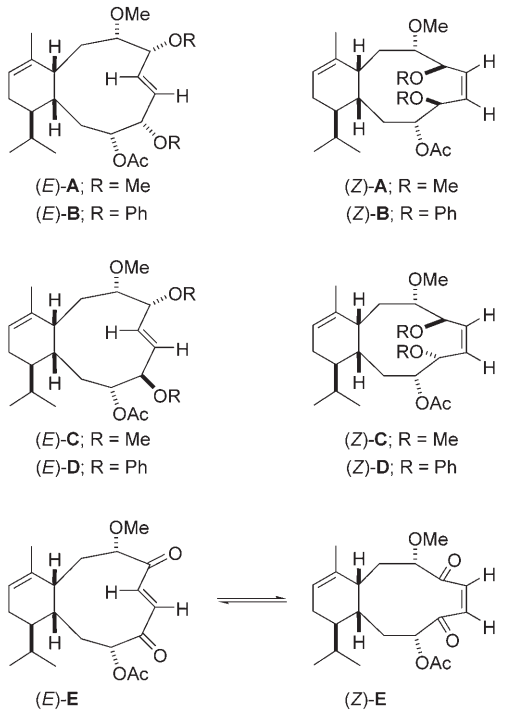
Scheme 4. Reagents and conditions: a) PMPOAllyl, *sec*-BuLi (1.4 M in cyclohexane), ^{d}Ipc$_2$BOMe, $BF_3{\cdot}Et_2O$, THF, −78°C→25°C, 40% **18**, 14% **19**; b) PivCl, DMAP, DIPEA, CH_2Cl_2, 25°C, 83%; c) cat. **13** (30% mol), toluene, 110°C, 6.5 h, 27% **21**, 15% **22**. PMP = *p*-methoxyphenyl; Piv = *tert*-BuCO; DMAP = 4-(dimethylamino)pyridine; DIPEA = diisopropylethylamine; Ipc = isopinocamphenyl.

pinene[19] to give the *syn* products **18** (40%) and **19** (14%) in an approximate 3:1 ratio. The major alcohol **18** was then transformed into the pivalate **20** (83%), and this diene was subjected to ring-closing metathesis under the same forcing conditions described above. Two compounds were obtained, both with the exact molecular ion (HRMS analysis) for the desired product: the structures were determined to be the

stereoisomer (*E*)-**21** ($^3J_{H\text{-}5/H\text{-}6}=17.0$ Hz) (27%)[20] together with the rearranged product **22** (15%),[21] originating from a ring-opening metathesis/ring-closing metathesis (ROM/RCM) process involving the trisubstituted double bond of the cyclohexene ring and the two terminal alkenes. Compound **21** was then transformed into the target molecule **3** by using the same sequence of reactions described in Scheme 3.

Molecular mechanics and semiempirical calculations: Molecular mechanics and semiempirical PM3[22] calculations were undertaken in order to investigate the stereochemical outcome of the RCM reactions and of the subsequent enedione isomerization (**16**→**4**).

Compounds **14**, **21**, **16**, and **4** were simplified into structures **A**–**E** (*E* and *Z* stereoisomers). The following changes were made to the protective groups to reduce the number of



rotatable bonds and low-quality torsional parameters: OPiv into OAc, OPMP into either OMe (**A** and **C**) or OPh (**B** and **D**), and OMOM into OMe. Initially, conformational searches were carried out with MacroModel[23] (MM2*, $CHCl_3$ GB/SA) on each of the structures **A**–**E**. In the case of structures **A** and **C**, only four low-quality torsional parameters were in use,[24] and therefore the quality of the calculations was considered acceptable (Table 1).

In the case of structures **B** and **D**, ten low-quality torsional parameters were in use,[25] in particular those relevant for the torsions around the allylic phenyl ethers, and therefore the quality of the calculations was considered unacceptable. In the case of structure **E**, six low-quality torsional parameters were in use,[26] in particular those relevant for the torsions around the enedione, and therefore the quality of the calculations was also considered unacceptable. The structures generated with MacroModel were then optimized at the PM3 level[22] with the Gaussian 03 package.[27] These calculations showed that the *Z* stereoisomers of structures **A**–**E** are consistently more stable than the *E* stereoisomers, with energy differences ranging from 5.7 to 17.1 kJ mol^{-1} (Table 1). This result is in agreement with our previous experimental observations and calculations, for which a number of similar but less densely functionalized structures (i.e. bearing protected and/or free alcohol functionalities at both the homoallylic positions and at only one allylic position) were shown to be consistently more stable as *Z* rather than as *E* stereoisomers.[9q] In all those cases, the exclusive formation of the *Z* isomer of the ten-membered carbocycles in the RCM reactions was interpreted as the result of thermodynamic control.[9q]

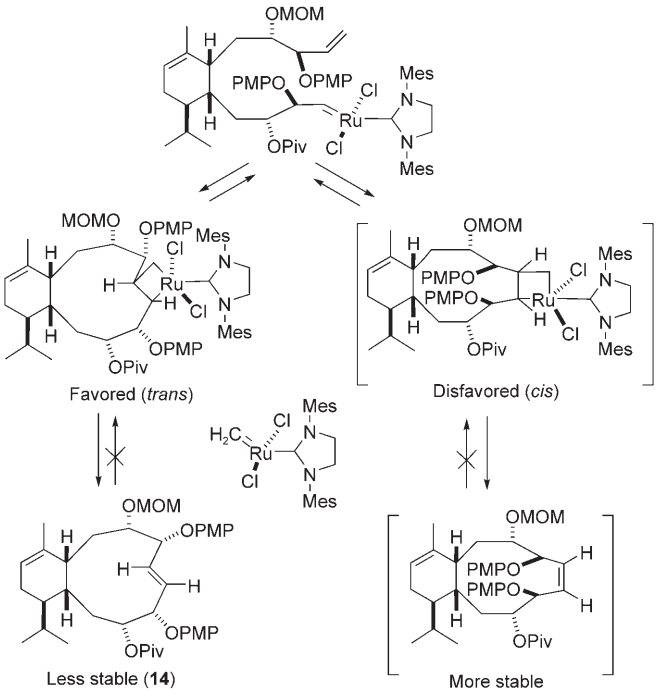
Table 1. Global minimum energy differences between the (*E*) and the (*Z*)-stereoisomers of structures **A**–**E**.

	E_E-E_Z (MM2*)[a]	E_E-E_Z (PM3)[a]		E_E-E_Z (MM2*)[a]	E_E-E_Z (PM3)[a]
A	6.6	15.0	**B**	−4.6[b]	17.1
C	7.9	6.2	**D**	−5.6[b]	8.0
E	21.7[b]	5.7			

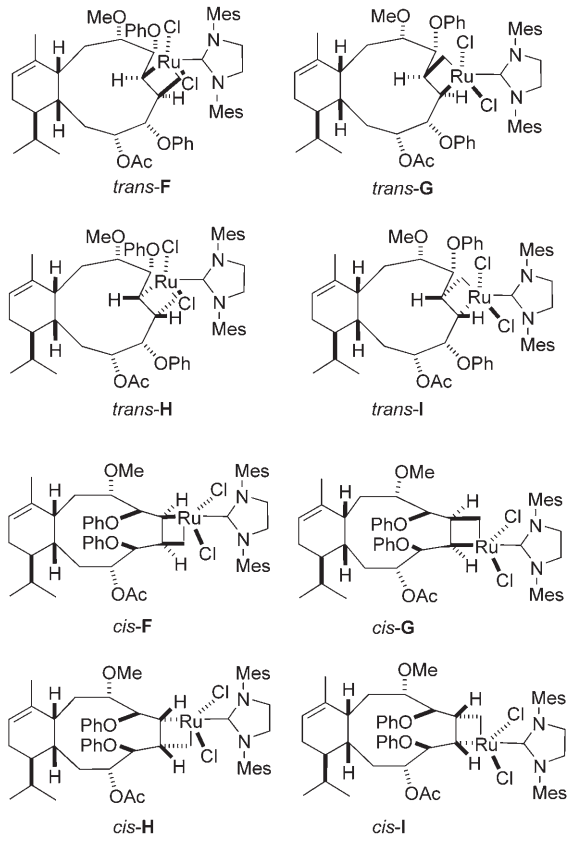
[a] Energy differences in kJ mol^{-1}. [b] See text for the presence of low-quality torsional parameters.

The reasons why the less stable *E* stereoisomers **14** and **21** were formed on this occasion and no trace of the more stable *Z* stereoisomer could be identified in the reaction mixture have been investigated in detail. Our working hypothesis is the following: the *trans*-ruthenacyclobutane intermediate is more stable than the *cis* isomer, leading to the less stable *E* stereoisomer under kinetic control.[28] Once formed, the *E* double bond of **14** (and **21**), flanked by two bulky -OPMP groups, is too sterically hindered to react again with the ruthenium–methylidene complex by means of [2+2] cycloaddition and cycloreversion (according to the generally accepted Hérisson–Chauvin mechanism),[29] thus arresting the equilibrium between the ring-closed and ring-opened products and inhibiting thermodynamic control (Scheme 5).

Density functional theory (DFT) calculations of the ruthenacyclobutane intermediates: Density functional theory (DFT) calculations were undertaken to determine the relative stabilities of the *trans*- and *cis*-ruthenacyclobutane intermediates (*trans*/*cis*-**F**–**I**). The core structure of the ruthenacyclobutane intermediate was taken from the structure calculated for the reaction of [$(H_2IMes)(PCy_3)(Cl_2)Ru{=}CH_2$] with ethyl vinyl ether, for which full DFT calculations had been carried out using the BP86 gradient-corrected density functional.[30] Preliminary conformational searches were carried out with MacroModel[23] (MM2*, $CHCl_3$ GB/SA) on each of the structures **F**–**I**, freezing the core ruthenacyclobutane fragment (including the mesityl-substituted *N*-heterocyclic carbene) in the original DFT-calculated geometry.[30,31]



Scheme 5. Working hypothesis for the RCM reaction under kinetic control, leading to the thermodynamically less stable *E* stereoisomer **14**.



These initial minimizations were important to relieve the nonbonded interactions between the sterically bulky mesityl groups and the densely functionalized ten-membered carbocycle. The resulting minima were then fully optimized by using DFT methods[32] at the B3LYP[33]/3–21G* level of theory (Table 2), and finally submitted to single-point energy calculations at the B3LYP/LANL2DZ[34]//B3LYP/3–21G* level (Table 3).

Table 2. Relative energies (B3LYP/3–21G*)[33] of the ruthenacyclobutane intermediates *trans*/cis-**F**–**I**.

	trans[a]	*cis*[a]		*trans*[a]	*cis*[a]
F	34.1	47.3	**G**	0.0	56.9
H	18.0	56.2	**I**	11.6	71.9

[a] Relative energies in kJ mol^{-1}.

Table 3. Relative energies (B3LYP/LANL2DZ)[34] of the ruthenacyclobutane intermediates *trans*/*cis*-**F**–**I**.

	trans[a]	*cis*[a]		*trans*[a]	*cis*[a]
F	13.4	50.3	**G**	6.5	55.7
H	6.1	56.1	**I**	0.0	67.9

[a] Relative energies in kJ mol^{-1}.

The calculations show that the *trans*-ruthenacyclobutane intermediates are consistently more stable than the corresponding *cis* isomers, in particular the lowest energy *trans* (*trans*-**I**) and *cis* (*cis*-**F**) structures have a 50.3 kJ mol^{-1} energy difference (Table 3). According to the generally accepted Hérisson–Chauvin mechanism,[29] the metathesis reaction consists of a series of formal [2+2] cycloadditions and cycloreversions. The overall process starts with olefin coordination to the transition-metal–carbene complex to form a π complex, followed by migratory insertion of the olefin into the metal–carbene bond to give a metallacyclobutane, breaking of two different bonds in the metallacyclobutane to form another π complex, and finally dissociation to yield the products. Experimental and theoretical studies on olefin methatesis have shown that the reaction proceeds through a phosphane dissociative mechanism,[35] that the olefin coordination to the tetracoordinate 14-electron ruthenium complex occurs *trans* to the ancillary ligand,[36] and that the ruthenacyclobutane is a real intermediate.[36,37] Recently, DFT calculations have been carried out to gain insight into the factors that govern the stereochemistry of the cycloolefin formed by a RCM reaction.[38] These studies have identified either the formation or the cleavage of the ruthenacyclobutane intermediate as the rate-determining step, which ultimately determines the stereochemical (*Z*/*E*) outcome of the cycloolefin under kinetic control, depending on the types of catalysts used, olefins, and reaction pathway.[38] Calculations performed on olefins lacking substitution at the allylic position (i.e., different from our case) suggest that with *N*-heterocyclic carbene (NHC)-based catalysts (e.g., the second-generation Grubbs catalyst), the rate-determining step is the cleavage of the ruthenacyclobutane intermediate.[36–38] This implies that the less stable *cis*-ruthenacyclobutane intermediates (from Tables 2 and 3) would face a smaller cleavage barrier compared to the more stable *trans*-ruthenacyclo-

butanes, thus determining the preferential formation of the (*Z*)-cycloolefin, which is not observed experimentally. However, DFT calculations for more hindered diene substrates (either methyl-disubstituted olefins[38] or cyclic with allylic substitution as in the case of norbornene[37]) have shown that the relative importance of the ruthenacycle formation and cleavage steps is inverted and the formation of the ruthenacyclobutane is the rate-determining step in those cases. The increased ruthenacycle formation barrier and decreased cleavage barrier are mainly due to the generation/release of repulsive nonbonded interactions during the formation/cleavage of the ruthenacyclobutane. This effect may also be present in the densely functionalized system described here, which has substitution at *both* the allylic and homoallylic positions of *both* olefinic fragments. If the rate-determining step is indeed the formation of the ruthenacyclobutane, there would be a diminished energy barrier and therefore a strong kinetic preference for the formation of the more stable *trans*-ruthenacyclobutane intermediate (Tables 2 and 3), which would lead to the observed (*E*)-cycloolefin product.

In summary, we have accomplished a formal total synthesis of eleutherobin (**2**) making use of: 1) multiple stereoselective titanium-mediated oxyallylations, 2) an unprecedented kinetically controlled second-generation Grubbs catalyzed RCM reaction of a densely functionalized diene bearing two allylic alcohols protected as *p*-methoxyphenyl (PMP) ethers, and 3) the isomerization of the *E* isomer of a ten-membered enedione to the more stable *Z* isomer. The unusual kinetically controlled RCM stereochemical outcome has been investigated using computational methods. Semiempirical PM3 calculations have shown that the *E* isomers of the ten-membered carbocycles resulting from the RCM reaction are less thermodynamically stable than the *Z* isomers ($E_E - E_Z = 6.2$–$17.1\ \mathrm{kJmol^{-1}}$). DFT calculations (B3LYP/LANL2DZ)[34] have shown that the *trans*-ruthenacyclobutane intermediates are more stable than the corresponding *cis* isomers (lowest energy $E_{cis} - E_{trans} = 50.3\ \mathrm{kJ\,mol^{-1}}$). The calculations lend support to a proposed mechanism where the more stable *trans*-ruthenacyclobutane intermediate leads to the less stable *E* stereoisomer under kinetic control.

Experimental Section

General procedures: All reactions were carried out in flame-dried glassware under argon atmosphere. All commercially available reagents were used as received. The solvents were dried by distillation over the following drying agents and were transferred under nitrogen: CH_3CN (CaH_2), CH_2Cl_2 (CaH_2), $(CH_2Cl)_2$ (CaH_2), MeOH (CaH_2), Et_3N (CaH_2), $i Pr_2EtN$ (CaH_2), $HN(TMS)_2$ (CaH_2), THF (Na), Et_2O (Na), benzene (Na), toluene (Na), *n*-hexane (Na), and xylenes (Na). Organic extracts were dried over anhydrous Na_2SO_4. Reactions were monitored by analytical thin-layer chromatography (TLC) by using silica gel 60 F_{254} precoated glass plates (0.25 mm thickness) or basic alumina supported on aluminium foils. TLC R_f values are reported; visualization was accomplished by irradiation with a UV lamp and/or staining with ceric ammonium molybdate (CAM) solution. Flash column chromatography was performed by using silica gel 60 Å, particle size 40–64 μm, following the procedure by Still and co-workers.[39]

Proton NMR spectra were recorded on 400, 300, or 200 MHz spectrometers. Proton chemical shifts are reported in ppm (δ) with the solvent reference relative to tetramethylsilane (TMS) employed as the internal standard ($CDCl_3$, $\delta = 7.26$ ppm; [D_6]DMSO, $\delta = 2.50$ ppm). The following abbreviations are used to describe spin multiplicity: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad signal, dd = doublet of doublets, dt = doublet of triplets, ddd = doublet of doublet of doublets. Carbon NMR spectra were recorded on 400 (100 MHz), 300 (75 MHz) or 200 MHz (50 MHz) spectrometers with complete proton decoupling. Carbon chemical shifts are reported in ppm (δ) relative to TMS with the respective solvent resonance as the internal standard ($CDCl_3$, $\delta = 77.0$). Optical rotation values were measured on an automatic polarimeter at the sodium D-line. Infrared spectra were recorded on a standard infrared spectrophotometer; peaks are reported in $\mathrm{cm^{-1}}$. High-resolution mass spectra (HRMS) were performed on a hybrid quadrupole time-of-flight mass spectrometer equipped with an ESI ion source. A Reserpine solution 100 $\mathrm{pg\,\mu L^{-1}}$ (about 100 $\mathrm{count\,s^{-1}}$), 0.1% HCOOH/CH_3CN 1:1, was used as reference compound (Lock Mass).

[(1*R*,5*R*,6*R*)-6-Dimethoxymethyl-5-isopropyl-2-methylcyclohex-2-enyl]-acetaldehyde (6): Aldehyde **6** was prepared on a multigram scale in six steps from *R*-(−)-carvone (30% overall yield) according to reference [9a,g].

{(1*R*,2*R*,6*R*)-6-Isopropyl-2-[(2*S*,3*R*)-2-methoxymethoxy-3-(4-methoxyphenoxy)pent-4-enyl]-3-methylcyclohex-3-enyl}acetaldehyde (11): Aldehyde **11** was prepared in seven steps from aldehyde **6** (49–50% overall yield) according to reference [9q].

(2*R*,3*S*)-1-{(1*R*,2*R*,6*R*)-6-Isopropyl-2-[(2*S*,3*R*)-2-methoxymethoxy-3-(4-methoxyphenoxy)pent-4-enyl]-3-methylcyclohex-3-enyl}-3-(4-methoxyphenoxy)pent-4-en-2-ol (12): *sec*-BuLi (1.4 M in cyclohexane, 714 μL, 1.00 mmol) was added to a cold (−78 °C), stirred solution of 1-allyloxy-4-methoxybenzene[40] (164 mg, 1.00 mmol) in THF (8.0 mL). After stirring for 1 h, the resulting orange solution (color is important) was transferred, through a cannula, to a cold (−78 °C) suspension of complex (*R*,*R*)-**7**[12] (613 mg, 1.00 mmol) in Et_2O (20.0 mL). The reaction mixture was stirred for 3.5 h at −78 °C (color changed from yellow to orange and finally dark brown), and then was treated with a solution of aldehyde **11** (269 mg, 0.6 mmol) in Et_2O (15.0 mL) and warmed to room temperature overnight. The reaction mixture was treated with a NH_4F aqueous solution (45%, 20 mL) and stirred for further 24 h. The organic phase was separated and the aqueous layer was extracted with EtOAc (2 × 50 mL). Purification of the crude product by flash chromatography (petroleum ether/EtOAc, 7:3) afforded alcohol **12** (300 mg, 83%) as a colorless oil. $R_f = 0.42$ (petroleum ether/EtOAc, 7:3); $[\alpha]_D^{20} = +29.7$ ($c = 1.72$ in EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 6.90$–6.74 (m, 8H), 5.97–5.83 (m, 2H), 5.40–5.25 (m, 5H), 4.88 (d, $J = 6.8$ Hz, 1H), 4.76 (d, $J = 6.8$ Hz, 1H), 4.72–4.64 (m, 1H), 4.43 (dd, $J = 7.1$, 4.4 Hz, 1H), 4.11–4.01 (m, 1H), 3.89 (dt, $J = 9.6$, 3.1 Hz, 1H), 3.77 (s, 6H), 3.36 (s, 3H), 2.39 (br, 1H), 2.10–1.47 (m, 13H), 0.94 (d, $J = 6.7$ Hz, 3H), 0.85 ppm (d, $J = 6.6$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 154.2$, 153.9, 152.2, 151.7, 136.7, 134.6, 134.4, 121.0, 120.1, 118.8, 117.7, 117.1, 114.5, 114.4, 97.4, 83.9, 82.7, 79.3, 71.0, 55.8, 55.6, 38.6, 35.0, 34.5, 30.9, 29.9, 27.0, 24.2, 22.6, 21.0 ppm; FT-IR (CCl_4): $\tilde{\nu} = 3598$, 3468, 3080, 3045, 2943, 2834, 2289, 2070, 2003, 1858, 1741, 1641, 1500, 1466, 1441, 1387, 1369, 1289, 1237, 1181, 1152, 1105, 1029, 930 $\mathrm{cm^{-1}}$; HRMS (ESI): calcd for $C_{36}H_{50}NaO_7$: 617.34487 [*M*+Na]$^+$; found: 617.34252 (resolution 19000).

(1*R*,2*S*)-1-{(1*R*,2*R*,6*R*)-6-Isopropyl-2-[(2*S*,3*R*)-2-methoxymethoxy-3-(4-methoxyphenoxy)pent-4-enyl]-3-methylcyclohex-3-enylmethyl}-2-(4-methoxyphenoxy)but-3-enyl ester of 2,2-dimethylpropionic acid (5): PivCl (51 μL, 0.41 mmol) was added to a stirred solution of alcohol **12** (82 mg, 0.14 mmol), DMAP (17 mg, 0.14 mmol), and DIPEA (122 μL, 0.70 mmol) in CH_2Cl_2 (5.0 mL). After stirring for 16 h, the reaction mixture was treated with a saturated $NaHCO_3$ aqueous solution (15 mL) and CH_2Cl_2 (15 mL) and stirred for further 15 min. The organic phase was separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). Purification of the crude product by flash chromatography (petroleum ether/EtOAc, 9:1) afforded compound **5** (89 mg, 96%) as a colorless oil.

$R_f = 0.47$ (petroleum ether/EtOAc, 7:3); $[\alpha]_D^{20} = +34.3$ ($c = 1.55$ in EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 6.91$–6.73 (m, 8H), 5.96–5.82 (m, 2H), 5.38–5.24 (m, 6H), 4.89 (d, $J = 6.7$ Hz, 1H), 4.81 (d, $J = 6.7$ Hz, 1H), 4.76 (dd, $J = 6.2$, 3.4 Hz, 1H), 4.59–4.51 (m, 1H), 3.96–3.89 (m, 1H), 3.77 (s, 3H), 3.76 (s, 3H), 3.39 (s, 3H), 2.33 (br, 1H), 2.11–2.00 (m, 1H), 1.92–1.58 (m, 10H), 1.51–1.42 (m, 1H), 1.17 (s, 9H), 0.93 (d, $J = 6.8$ Hz, 3H), 0.85 ppm (d, $J = 6.6$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta =$ 177.8, 154.2, 153.9, 152.3, 152.2, 137.0, 134.6, 120.9, 119.4, 118.9, 117.9, 117.2, 114.4, 97.4, 82.5, 82.4, 79.1, 72.6, 55.8, 55.6, 38.9, 38.3, 35.1, 34.9, 30.6, 27.6, 27.2, 27.1, 24.2, 22.7, 20.9 ppm; FT-IR (CCl_4): $\tilde{\nu} = 3046$, 2960, 2834, 2305, 2004, 1857, 1729, 1559, 1505, 1479, 1442, 1423, 1387, 1369, 1229, 1181, 1157, 1104, 1040, 930 cm^{-1}; HRMS (ESI): calcd for $C_{41}H_{58}NaO_8$: 701.40239 $[M+Na]^+$; found: 701.40002 (resolution 16700).

(*E*)-(4*R*,4a*R*,6*R*,7*S*,10*R*,11*S*,12a*R*)-4-Isopropyl-11-methoxymethoxy-7,10-bis(4-methoxyphenoxy)-1-methyl-3,4,4a,5,6,7,10,11,12,12a-decahydrobenzocyclodecen-6-yl ester of 2,2-dimethylpropionic acid (14): A freshly prepared solution of the second-generation Grubbs catalyst **13** (16 mg, 0.019 mmol) in toluene (3.4 mL) was added through a syringe pump over a period of 2.5 h to a heated (110 °C), stirred solution of compound **5** (42 mg, 0.062 mmol) in toluene (6.8 mL). After 4 h at 110 °C, the reaction mixture was cooled to room temperature, treated with DMSO[41] (67 μL, 0.94 mmol) and stirred for 15 h at room temperature. Purification of the crude product by flash chromatography over two consecutive columns (first: petroleum ether/EtOAc, 85:15; second: CH_2Cl_2/iPr$_2$O, 97:3) afforded compound **14** (26 mg, 64%) as a white amorphous solid. $R_f =$ 0.46 (petroleum ether/EtOAc, 8:2); $[\alpha]_D^{20} = +38.4$ ($c = 1.27$ in EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 6.89$–6.64 (m, 8H), 5.96 (br, 1H), 5.71 (br, 1H), 5.29 (br, 1H), 5.04 (br, 2H), 4.86–4.63 (m, 3H), 3.85 (br, 1H), 3.75 (s, 3H), 3.73 (s, 3H), 3.28 (br, 3H), 2.44 (br, 1H), 2.17–1.20 (m, 12H), 1.13 (s, 9H), 0.91 (d, $J = 6.8$ Hz, 3H), 0.74 ppm (br, 3H); ^{13}C NMR (100 MHz, C_6D_6): $\delta =$ 179.8, 154.8, 154.5, 153.0, 140.8, 135.2, 127.0, 120.9, 117.5, 117.3, 115.1, 95.7, 81.0, 79.1, 78.5, 76.6, 55.6, 55.3, 41.0, 40.3, 39.1, 37.0, 32.5, 27.4, 26.9, 25.1, 24.3, 21.2, 14.1 ppm; FT-IR (CCl_4): $\tilde{\nu} =$ 2960, 2932, 2833, 2289, 2009, 1854, 1722, 1548, 1508, 1479, 1464, 1441, 1396, 1387, 1368, 1284, 1230, 1181, 1156, 1103, 1008, 917 cm^{-1}; HRMS (ESI): calcd for $C_{39}H_{54}NaO_8$: 673.37109 $[M+Na]^+$; found: 673.36999 (resolution 18000).

Minor by-products (5–10%) were tentatively identified by HRMS analysis as the corresponding mono- and dibenzylidene derivatives of the starting diene **5**, arising from the cross-metathesis reaction promoted by the second-generation Grubbs catalyst **13**. Monobenzylidene derivative: HRMS (ESI): calcd for $C_{47}H_{62}NaO_8$: 777.43369 $[M+Na]^+$; found: 777.43360 (resolution 14700). Dibenzylidene derivative: HRMS (ESI): calcd for $C_{53}H_{66}NaO_8$: 853.46499 $[M+Na]^+$; found: 853.46552 (resolution 14700).

(*E*)-(4*R*,4a*R*,7*S*,10*R*,11*S*,12a*R*)-7,10-Dihydroxy-4-isopropyl-11-methoxymethoxy-1-methyl-3,4,4a,5,6,7,10,11,12,12a-decahydrobenzocyclodecen-6-yl ester of 2,2-dimethylpropionic acid (15): Ceric ammonium nitrate (92 mg, 0.168 mmol) was added in one portion to a cold (0 °C), stirred solution of compound **14** (26 mg, 0.04 mmol) in CH_3CN/H_2O (1.38 mL, *v*/*v*: 4:1). After 2 min, the reaction mixture was treated with water (5 mL) and iPr$_2$O (5 mL). The aqueous phase was separated and the organic layer was extracted with water (2×5 mL). Purification of the crude product by flash chromatography (*n*-hexane/EtOAc, 6:4), followed by further purification by flash chromatography (CH_2Cl_2/EtOAc, 7:3) afforded compound **15** (14 mg, 80%) as a white amorphous solid. $R_f = 0.20$ (*n*-hexane/EtOAc, 6:4); $[\alpha]_D^{20} = +25.5$ ($c = 0.80$ in EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 6.15$–5.97 (m, 1H), 5.63–5.44 (m, 1H), 5.26 (br, 1H), 4.83–4.53 (m, 5H), 3.81 (br, 1H), 3.41 (s, 3H), 2.70 (br, 1H), 2.26–1.36 (m, 14H), 1.23 (s, 9H), 0.86 (d, $J = 6.4$ Hz, 3H), 0.67 ppm (br, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta =$ 177.3, 140.4, 132.7, 126.9, 120.6, 94.1, 78.5, 77.1, 71.6, 70.4, 55.7, 39.7, 39.0, 36.1, 29.9, 29.7, 27.2, 26.8, 26.5, 24.5, 24.1, 20.9, 13.7 ppm; FT-IR (CCl_4): $\tilde{\nu} =$ 3620, 3589, 2960, 2290, 2207, 1856, 1727, 1549, 1396, 1369, 1258, 1217, 1152, 1098, 1070, 1010 cm^{-1}; HRMS (ESI): calcd for $C_{25}H_{42}NaO_6$: 461.28736 $[M+Na]^+$; found: 461.28555 (resolution 21900).

(*E*)-(4*R*,4a*R*,11*S*,12a*R*)-4-Isopropyl-11-methoxymethoxy-1-methyl-7,10-dioxo-3,4,4a,5,6,7,10,11,12,12a-decahydrobenzocyclodecen-6-yl ester of 2,2-dimethylpropionic acid (16), **(*Z*)-(4*R*,4a*R*,11*S*,12a*R*)-4-isopropyl-11-methoxymethoxy-1-methyl-7,10-dioxo-3,4,4a,5,6,7,10,11,12,12a-decahydrobenzocyclodecen-6-yl ester of 2,2-dimethylpropionic acid (4), and (4*R*,5*R*,9*R*,11*S*)-1,12-dihydroxy-5-isopropyl-11-methoxymethoxy-8-methyl-15-oxa-tricyclo[10.2.1.0^{4,9}]pentadeca-7,13-dien-2-yl ester of 2,2-dimethylpropionic acid (17)**: DMP (60 mg, 0.14 mmol) was added to a stirred solution of compound **15** (12.4 mg, 0.028 mmol) in CH_2Cl_2 (375 μL). After stirring for 3 h, the reaction mixture was treated with a NaOH aqueous solution (1.0 M, 2 mL) and CH_2Cl_2 (2 mL) and stirred for further 15 min. The organic phase was separated and the aqueous layer was extracted with CH_2Cl_2 (4×3 mL). Purification of the crude product by flash chromatography afforded the enedione (*E*)-**16** (10.9 mg, 90%) as a white amorphous solid.

Compound (*E*)-16: $R_f = 0.34$ (*n*-hexane/EtOAc, 8:2); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.07$ (br, 1H), 6.64 (d, $J = 17.3$ Hz, 1H), 5.51 (br, 1H), 5.38 (br, 1H), 4.76 (d, $J = 7.2$ Hz, 1H), 4.73 (d, $J = 7.2$ Hz, 1H), 4.56 (d, $J =$ 9.2 Hz, 1H), 3.44 (s, 3H), 2.49 (br, 1H), 2.15–1.50 (m, 11H), 1.41 (br, 1H), 1.29 (s, 9H), 0.92 (d, $J = 6.4$ Hz, 3H), 0.79 ppm (d, $J = 6.4$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta =$ 198.2, 195.9, 178.2, 137.2, 134.8, 122.2, 121.2, 95.6, 80.2, 76.8, 56.1, 39.2, 38.7, 37.1, 36.9, 34.2, 33.1, 29.7, 27.1, 26.5, 24.6, 23.3, 20.7 ppm; FT-IR (CCl_4): $\tilde{\nu} = 2962$, 2932, 2284, 2007, 1741, 1725, 1548, 1397, 1388, 1370, 1259, 1145, 1099, 1062, 1008 cm^{-1}; HRMS (ESI): calcd for $C_{25}H_{38}NaO_6$: 457.25606 $[M+Na]^+$; found: 457.25503 (resolution 25900).

While recording the ^{1}H NMR spectrum of compound **16** in $CDCl_3$, the *E* enedione cleanly isomerized to the more stable enedione (*Z*)-**4** ($t_{1/2} =$ 63 h). A complete isomerization of the enedione (*E*)-**16** to (*Z*)-**4** was accomplished by addition of a catalytic amount (10 mol%) of I_2 in $CDCl_3$ at room temperature (24 h).

Compound (*Z*)-4: $R_f = 0.34$ (*n*-hexane/EtOAc, 8:2); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.20$ (d, $J = 14.0$ Hz, 1H), 6.13 (d, $J = 14.0$ Hz, 1H), 5.53 (d, $J = 9.2$ Hz, 1H), 5.34 (br, 1H), 4.75 (d, $J = 6.4$ Hz, 1H), 4.69 (d, $J =$ 6.4 Hz, 1H), 4.20 (dd, $J = 12.0$, 5.8 Hz, 1H), 3.40 (s, 3H), 2.12 (br, 1H), 2.05–1.53 (m, 11H), 1.35 (br, 1H), 1.27 (s, 9H), 0.90 (d, $J = 6.9$ Hz, 3H), 0.74 ppm (d, $J = 6.8$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 204.4$, 196.7, 177.6, 138.1, 137.2, 133.4, 120.6, 96.6, 84.3, 73.2, 56.1, 38.7, 37.1, 36.9, 34.2, 33.0, 30.2, 27.1, 26.4, 24.5, 22.7, 20.9, 14.1 ppm; FT-IR (CCl_4): $\tilde{\nu} = 2962$, 2932, 2290, 2204, 1744, 1701, 1547, 1479, 1463, 1397, 1388, 1379, 1369, 1254, 1217, 1146, 1100, 1061, 1006 cm^{-1}; HRMS (ESI): calcd for $C_{25}H_{38}NaO_6$: 457.25606 $[M+Na]^+$; found: 457.25582 (resolution 25800).

Bis-hemiacetal **17** was obtained after flash chromatography of the *Z* enedione **4**.

Compound 17: $R_f = 0.27$ (*n*-hexane/EtOAc, 6:4); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 6.29$ (d, $J = 5.8$ Hz, 1H), 6.18 (d, $J = 5.8$ Hz, 1H), 5.25 (br, 1H), 5.02–4.96 (m, 1H), 4.83 (d, $J = 6.4$ Hz, 1H), 4.73 (d, $J = 6.4$ Hz, 1H), 4.08 (br, 2H), 3.96 (dd, $J = 11.6$, 2.4 Hz, 1H), 3.44 (s, 3H), 2.60 (br, 1H), 1.88–1.48 (m, 10H), 1.40–1.14 (m, 11H), 0.88 (d, $J = 6.8$ Hz, 3H), 0.71 ppm (d, $J = 6.4$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta =$ 178.8, 138.8, 133.1, 132.2, 119.2, 111.7, 110.3, 96.6, 80.6, 76.6, 55.7, 39.5, 38.7, 37.7, 37.5, 33.5, 31.5, 26.9, 26.6, 24.3, 22.8, 21.2, 14.7 ppm; FT-IR (CCl_4): $\tilde{\nu} =$ 3430, 3028, 2960, 2929, 2289, 2006, 1728, 1548, 1397, 1388, 1368, 1260, 1217, 1151, 1102, 1008, 809 cm^{-1}; HRMS (ESI): calcd for $C_{25}H_{40}NaO_7$: 475.26662 $[M+Na]^+$; found: 475.26681 (resolution 25800).

(1*S*,3*R*,7*R*,8*R*,10*R*,11*S*)-11-Hydroxy-7-isopropyl-4-methyl-14-oxo-15-oxa-tricyclo[9.3.1.0^{3,8}]pentadeca-4,12-dien-10-yl ester of 2,2-dimethylpropionic acid (3): Me_2S (15.4 mg, 0.25 mmol) and $BF_3{\cdot}OEt_2$ (42.7 mg, 0.30 mmol) were added to a cold (−78 °C), stirred solution of a mixture of **16**/**4**/**17** (12.0 mg, 0.028 mmol based on **4**) in CH_2Cl_2 (920 μL). The reaction was slowly warmed to −20 °C (over 3 h), treated with a saturated $NaHCO_3$ aqueous solution (5 mL), and warmed to room temperature under vigorous stirring. The organic phase was separated and the aqueous layer was extracted with CH_2Cl_2 (3×5 mL). Purification of the crude product by flash chromatography (*n*-hexane/EtOAc, 9:1) afforded the Danishefsky key-intermediate **3**[8c] (8.4 mg, 78%) as a white amorphous solid. $R_f =$ 0.25 (*n*-hexane/EtOAc, 8:2); $[\alpha]_D^{20} = -60.0$ ($c = 0.60$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.08$ (d, $J = 10.5$ Hz, 1H), 6.19 (d, $J = 10.5$ Hz, 1H), 5.35 (br, 1H), 4.88 (d, $J = 7.6$ Hz, 1H), 4.67 (t, $J = 4.4$ Hz, 1H), 3.27 (br, 1H), 2.47–2.28 (m, 1H), 2.10–1.65 (m, 7H), 1.65–1.32 (m, 2H), 1.58

(s, 3H), 1.26 (s, 9H), 0.92 (d, $J=6.9$ Hz, 3H), 0.76 ppm (d, $J=6.9$ Hz, 3H); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=7.08$ (d, $J=10.5$ Hz, 1H), 6.19 (d, $J=10.5$ Hz, 1H), 5.35 (br, 1H), 4.88 (d, $J=7.6$ Hz, 1H), 4.67 (t, $J=4.4$ Hz, 1H), 3.31 (br, 1H), 2.46–2.33 (m, 1H), 2.11–1.69 (m, 7H), 1.65–1.38 (m, 2H), 1.58 (s, 3H), 1.26 (s, 9H), 0.92 (d, $J=6.8$ Hz, 3H), 0.76 ppm (d, $J=6.8$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=195.5$, 177.4, 151.0, 126.7, 121.6, 92.5, 78.6, 77.7, 38.8, 38.1, 32.8, 27.0, 26.7, 24.0, 21.3, 21.2 ppm; FT-IR (CCl_4): $\tilde{\nu}=3589$, 3395, 3028, 2961, 2930, 2872, 2289, 2205, 1856, 1731, 1693, 1549, 1480, 1462, 1254, 1217, 1147, 1109, 1067, 1006, 980 cm^{-1}; HRMS (ESI): calcd for $C_{23}H_{34}NaO_5$: 413.22984 $[M+Na]^+$; found: 413.22821 (resolution 24300).

(2*R*,3*R*)-1-{(1*R*,2*R*,6*R*)-6-Isopropyl-2-[(2*S*,3*R*)-2-methoxymethoxy-3-(4-methoxyphenoxy)pent-4-enyl]-3-methylcyclohex-3-enyl}-3-(4-methoxyphenoxy)pent-4-en-2-ol (18) and (2*S*,3*S*)-1-{(1*R*,2*R*,6*R*)-6-isopropyl-2-[(2*S*,3*R*)-2-methoxymethoxy-3-(4-methoxyphenoxy)pent-4-enyl]-3-methylcyclohex-3-enyl}-3-(4-methoxyphenoxy)pent-4-en-2-ol (19): *sec*-BuLi (1.4 M in cyclohexane, 280 μL, 0.39 mmol) was added to a cold (−78 °C), stirred solution of 1-allyloxy-4-methoxybenzene[40] (77.2 mg, 0.47 mmol) in THF (1.2 mL). After stirring for 1 h at −78 °C, the resulting orange solution (color is important) was treated with a solution of ^{d}Ipc$_2$BOMe[19] (1.0 M in THF, 390 μL, 0.39 mmol), and stirred for further 1 h. $BF_3{\cdot}Et_2O$ (63 μL, 0.50 mmol) and aldehyde **11** (68 mg, 0.16 mmol) were subsequently added and the resulting solution was warmed to room temperature overnight. The mixture was then treated with a NaOH aqueous solution (6.0 M, 1.5 mL), H_2O_2 (36%, 1.5 mL) and stirred for further 8 h. The organic phase was separated and the aqueous layer was extracted with iPr$_2$O (3×5 mL). Purification of the crude product by flash chromatography (petroleum ether/EtOAc, 85:15) afforded alcohols **18** (37.6 mg, 40%) and **19** (13.2 mg, 14%) as colorless oils.

Compound 18: $R_f=0.31$ (petroleum ether/EtOAc, 85:15); $[\alpha]_D^{20}=+39.7$ ($c=1.06$ in EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=6.90$–6.76 (m, 8H), 5.95–5.82 (m, 2H), 5.39–5.24 (m, 5H), 4.81 (d, $J=6.8$ Hz, 1H), 4.70–4.63 (m, 2H), 4.35 (dd, $J=6.2$, 6.2 Hz, 1H), 3.91 (br, 1H), 3.83–3.74 (m, 7H), 3.35 (s, 3H), 2.37 (br, 2H), 2.02 (br, 2H), 1.95–1.70 (m, 5H), 1.70–1.55 (m, 3H), 1.55–1.44 (m, 2H), 0.93 (d, $J=6.8$ Hz, 3H), 0.86 ppm (d, $J=6.4$ Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta=154.3$, 153.9, 152.3, 151.9, 136.9, 134.9, 134.6, 121.1, 119.5, 118.8, 117.5, 117.2, 114.5, 114.4, 97.2, 84.0, 82.6, 79.2, 71.4, 55.8, 55.6, 38.6, 35.0, 34.6, 30.8, 30.3, 27.1, 24.2, 22.6, 21.0, 17.3 ppm; FT-IR (CCl_4): $\tilde{\nu}=3585$, 2960, 2834, 2291, 2004, 1856, 1548, 1507, 1465, 1442, 1226, 1181, 1151, 1103, 1010, 930 cm^{-1}; HRMS (ESI): calcd for $C_{36}H_{50}NaO_7$: 617.34487 $[M+Na]^+$; found: 617.34252 (resolution 18900).

Compound 19: $R_f=0.23$ (petroleum ether/EtOAc, 85:15); $[\alpha]_D^{20}=+3.6$ ($c=0.97$ in EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=6.95$–6.74 (m, 8H), 5.98–5.78 (m, 2H), 5.40–5.26 (m, 5H), 4.92–4.84 (m, 2H), 4.82 (d, $J=6.8$ Hz, 1H), 4.32–4.23 (m, 1H), 4.01–3.95 (m, 1H), 3.79–3.77 (m, 7H), 3.30 (s, 3H), 2.56–2.39 (m, 2H), 2.20 (br, 1H), 2.15–2.04 (m, 1H), 2.04–1.87 (m, 2H), 1.80–1.50 (m, 5H), 1.50–1.30 (m, 3H), 0.94 (d, $J=6.8$ Hz, 3H), 0.90 ppm (d, $J=6.4$ Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta=154.2$, 153.8, 152.5, 151.9, 135.6, 135.2, 134.7, 120.7, 119.4, 118.1, 117.5, 116.9, 114.5, 98.0, 84.7, 82.2, 79.1, 71.3, 55.6, 39.7, 33.1, 31.0, 29.3, 28.5, 27.6, 24.0, 22.1, 21.2, 20.6 ppm; FT-IR (CCl_4): $\tilde{\nu}=3592$, 2959, 2833, 2288, 2003, 1855, 1741, 1544, 1503, 1465, 1441, 1421, 1386, 1372, 1232, 1181, 1151, 1105, 1041, 930 cm^{-1}; HRMS (ESI): calcd for $C_{36}H_{50}NaO_7$: 617.34487 $[M+Na]^+$; found: 617.34336 (resolution 18900).

(1*R*,2*R*)-1-{(1*R*,2*R*,6*R*)-6-Isopropyl-2-[(2*S*,3*R*)-2-methoxymethoxy-3-(4-methoxyphenoxy)pent-4-enyl]-3-methylcyclohex-3-enylmethyl}-2-(4-methoxyphenoxy)but-3-enyl ester of 2,2-dimethylpropionic acid (20): PivCl (67 μL, 0.54 mmol) was added to a stirred solution of compound **18** (107 mg, 0.18 mmol), DMAP (22 mg, 0.18 mmol), and DIPEA (157 μL, 0.90 mmol) in CH_2Cl_2 (11.0 mL). After 7 h, the reaction mixture was treated with a saturated $NaHCO_3$ aqueous solution (10 mL) and stirred for further 15 min. The organic phase was separated and the aqueous layer was extracted with CH_2Cl_2 (3×10 mL). Purification of the crude product by flash chromatography (petroleum ether/EtOAc, 9:1) afforded compound **20** (101 mg, 83%) as a colorless oil. $R_f=0.57$ (petroleum ether/EtOAc, 9:1); $[\alpha]_D^{20}=+66.3$ ($c=1.32$ in EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=6.95$–6.75 (m, 8H), 5.94–5.80 (m, 2H), 5.41–5.24 (m, 6H), 4.77 (br, 1H), 4.72 (d, $J=6.7$ Hz, 1H), 4.68–4.59 (m, 2H), 3.88–3.73 (m, 7H), 3.31 (s, 3H), 2.35 (br, 1H), 2.14–2.03 (m, 1H), 1.92–1.55 (m, 10H), 1.46–1.36 (m, 1H), 1.21 (s, 9H), 0.94 (d, $J=6.7$ Hz, 3H), 0.84 ppm (d, $J=6.6$ Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta=177.9$, 154.0, 153.8, 152.3, 152.0, 136.6, 134.6, 133.7, 120.9, 118.8, 117.1, 116.9, 114.5, 114.3, 97.3, 82.1, 79.8, 79.1, 72.4, 55.7, 55.6, 38.9, 38.7, 34.6, 34.4, 30.1, 27.2, 27.1, 27.0, 24.1, 22.6, 20.8, 17.8 ppm; FT-IR (CCl_4): $\nu=2957$, 2833, 2290, 2005, 1857, 1727, 1549, 1509, 1479, 1465, 1441, 1407, 1396, 1386, 1368, 1281, 1223, 1181, 1155, 1105, 1042, 929 cm^{-1}; HRMS (ESI): calcd for $C_{41}H_{58}NaO_8$: 701.40239 $[M+Na]^+$; found: 701.40172 (resolution 16600).

(*E*)-(4*R*,4a*R*,6*R*,7*R*,10*R*,11*S*,12a*R*)-4-Isopropyl-11-methoxymethoxy-7,10-bis(4-methoxyphenoxy)-1-methyl-3,4,4a,5,6,7,10,11,12,12a-decahydrobenzocyclodecen-6-yl ester of 2,2-dimethylpropionic acid (21) and (*Z*)-(1*R*,2*R*,6*R*,7*R*)-6-isopropyl-7-[(1*R*,4*R*,5*S*)-5-methoxymethoxy-4-(4-methoxyphenoxy)-2-methylcyclohex-2-enyl]-2-(4-methoxyphenoxy)cyclooct-3-enyl ester of 2,2-dimethylpropionic acid (22): A freshly prepared solution of the second-generation Grubbs catalyst **13** (13 mg, 0.015 mmol) in toluene (3.3 mL) was added, through a syringe pump over a period of 2 h, to a heated (110 °C), stirred solution of compound **20** (35 mg, 0.051 mmol) in toluene (3.2 mL). After 4.5 h at 110 °C, the reaction mixture was cooled to room temperature, treated with DMSO[41] (54 μL, 0.75 mmol) and stirred for 15 h at room temperature. Purification of the crude product by flash chromatography (CH_2Cl_2/iPr$_2$O, 97:3) afforded compound **21** (9 mg, 27%) as a white amorphous solid and compound **22** (5 mg, 15%) as a colorless oil.

Compound 21: $R_f=0.47$ (petroleum ether/EtOAc, 8:2); $[\alpha]_D^{20}=-17.6$ ($c=1.12$ in EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=6.95$–6.72 (m, 8H), 5.87 (dd, $J=17.0$, 4.2 Hz, 1H), 5.60 (dd, $J=17.0$, 9.1 Hz, 1H), 5.33 (br, 1H), 5.13 (br, 1H), 4.86 (br, 1H), 4.78 (d, $J=7.2$ Hz, 1H), 4.70 (d, $J=7.2$ Hz, 1H), 4.51 (dd, $J=8.2$, 8.2 Hz, 1H), 3.80 (s, 3H), 3.78 (s, 3H), 3.61 (br, 1H), 3.33 (s, 3H), 2.29 (br, 1H), 2.24–1.94 (m, 4H), 1.91–1.60 (m, 7H), 1.53 (br, 1H), 1.14 (s, 9H), 0.98 (d, $J=8.0$ Hz, 3H), 0.93 ppm (d, $J=8.0$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=171.7$, 154.1, 152.4, 151.9, 138.0, 133.5, 128.4, 122.5, 117.1, 116.5, 114.6, 114.4, 95.7, 85.0, 80.3, 76.9, 75.4, 55.7, 55.4, 40.4, 38.7, 35.6, 29.4, 29.0, 27.1, 25.4, 22.0, 20.2 ppm; FT-IR (CCl_4): $\tilde{\nu}=2959$, 2931, 2289, 2003, 1856, 1728, 1550, 1507, 1464, 1441, 1368, 1227, 1153, 1105, 1006, 816 cm^{-1}; HRMS (ESI): calcd for $C_{39}H_{54}NaO_8$: 673.37109 $[M+Na]^+$; found: 673.36808 (resolution 17200).

Compound 22: $R_f=0.40$ (petroleum ether/EtOAc, 8:2); $[\alpha]_D^{20}=-24.6$ ($c=0.63$ in EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=6.95$–6.78 (m, 8H), 6.04–5.94 (m, 1H), 5.66 (dd, $J=11.0$, 7.0 Hz, 1H), 5.57 (br, 1H), 5.32–5.25 (m, 1H), 5.01 (br, 1H), 4.75–4.66 (m, 3H), 4.25 (br, 1H), 3.79 (s, 3H), 3.77 (s, 3H), 3.33 (s, 3H), 2.65 (br, 2H), 2.42 (br, 1H), 2.33–2.10 (m, 3H), 1.96 (br, 1H), 1.85–1.67 (m, 5H), 1.38–1.26 (m, 1H), 1.18 (s, 9H), 1.05 (d, $J=6.8$ Hz, 3H), 1.03 ppm (d, $J=6.8$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=177.8$, 154.0, 152.9, 140.4, 122.9, 117.1, 116.5, 114.7, 114.6, 95.6, 74.2, 71.3, 55.7, 55.4, 44.9, 39.0, 29.7, 29.1, 28.3, 27.3, 24.2, 23.1, 22.9 ppm; FT-IR (CCl_4): $\tilde{\nu}=2956$, 2833, 2289, 2004, 1855, 1729, 1553, 1504, 1479, 1465, 1441, 1396, 1368, 1226, 1180, 1152, 1104, 1043, 1007, 917 cm^{-1}; HRMS (ESI): calcd for $C_{39}H_{54}NaO_8$: 673.37109 $[M+Na]^+$; found: 673.36828 (resolution 17300).

Molecular mechanics and semiempirical calculations: The potential-energy surface of structures **A**–**E** (*Z* and *E* stereoisomers) was searched using Monte Carlo[23b] conformational searches with MacroModel (v8.5)[23a] running on a 3.0 GHz Intel Pentium 4 with LINUX Red Hat 9 operating system. The calculations were performed with the MM2* force field using the GB/SA continuum solvent model for $CHCl_3$.[23c] Interconversion of ring structures was enabled by using the ring-opening method of Still.[42] Ring-closure bonds were defined for both the six- and ten-membered rings present in structures **A**–**E**. Each search was run in blocks of 15000 steps until convergence was reached, that is, no new structures were found and the global minimum energy remained constant throughout the search. Typically, 50000–60000 steps were enough to ensure convergence. Each new cycle used as input the results of the previous cycle and different ring-closure bond choices were used. During the search, structures with energy 20 kJ mol^{-1} higher than the current global minimum were discarded. Structures were fully minimized for up to 5000

steps until the gradient was less than 0.05 kJ Å^{-1} mol^{-1} by using the Polak–Ribiere conjugate gradient method.[43] Redundant conformations were removed after heavy atom superimposition (RMSD cutoff = 0.25 Å). The lowest energy conformers obtained with MacroModel for the *Z* and the corresponding *E* stereoisomers of structures **A**–**E** (using a 20.0 kJ mol^{-1} energy window from the global minima) were then optimized at the PM3 level[22] by using the Gaussian 03 package.[27]

DFT calculations of the ruthenacyclobutane intermediates: Structures *trans* **F–I** and *cis* **F–I** used as input for the quantum mechanical calculations were generated through Monte Carlo[23b] conformational searches carried out with MacroModel (v9.0)[23] running on a 3.2 GHz Intel Pentium IV computer under Linux Fedora Core 3. The core ruthenacycle structure was taken from reference [30] and was frozen during the searches,[31] which were performed with the MM2* force field using the GB/SA continuum solvent model for $CHCl_3$,[23c] as described in the previous section. Each search was run in blocks of 10000 steps until convergence was reached. Typically, 20000–30000 steps were sufficient to ensure convergence. The lowest energy conformers for *trans* **F–I** and *cis* **F–I** generated during the search were optimized using the DFT method[32] at the B3LYP[33]/3–21G* level of theory. Single-point energy calculations were carried out at the B3LYP/LANL2DZ[34]//B3LYP/3–21G* level. All quantum mechanical calculations were carried out with the Gaussian 03 package.[27]

Acknowledgements

We thank the European Commission for financial support (IHP Network grant "Design and synthesis of microtubule stabilizing anticancer agents" HPRN-CT-2000–00018) and for postdoctoral fellowships to L.C. (HPRN-CT-2000–00018) and O.S. ("Marie Curie" MEIF-CT-2003–500880). We also gratefully acknowledge the Spanish "Ministerio de Ciencia y Tecnologia" for a "Ramon y Cajal" fellowship to A.M.C., "Merck Research Laboratories" (Merck's Academic Development Program Award to C. G.) and Università degli Studi di Milano for financial support and for graduate fellowships (to D.C. and L.P.). We thank Dr. Raphael Beumer, Dr. Pau Bayón, Dr. Joachim Telser, and Dr. Fabienne Pradaux for preliminary experiments related to this work, and Dr. Nicola Mongelli (Nerviano Medical Science) and Prof. Jaume Vilarrasa (University of Barcelona) for inspiring discussions.

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[21] In the case of compound **22**, complete proton resonance assignments were made with the aid of COSY, TOCSY, and HSQC experiments. The ^{1}H NMR spectrum (400 MHz) showed the following signals due to the three olefinic protons: a multiplet at $\delta = 6.04$–5.94, a doublet of doublets at $\delta = 5.66$ (dd, 1H, $J = 11.0$, 7.0 Hz) indicating the presence of a *Z* double bond, and a broad signal at $\delta = 5.57$ ppm. With the aid of the COSY spectrum, the signal at $\delta = 5.66$ ppm was assigned to H-5, due to the correlation with the multiplet at $\delta =$ 5.01 ppm (H-4), which, in turn, had a coupling with the multiplet at $\delta = 5.32$–5.25 ppm (H-3). Furthermore, the COSY spectrum showed a coupling between the signal at $\delta = 5.66$ ppm (H-5) and the multiplet at $\delta = 6.04$–5.94 ppm, thus assigning the other proton of the *Z* double bond (H-12); consequently, the signal at $\delta = 5.57$ ppm was assigned to the proton of the trisubstituted double bond (H-6). The signal at $\delta = 6.04$–5.94 ppm was assigned to proton H-12 due to the couplings with two different signals at $\delta = 2.7$ and 2.2 ppm (the two diastereotopic protons H-13$_a$ and H-13$_b$). The signal of the proton of the trisubstituted double bond (H-6, $\delta = 5.57$ ppm) showed a coupling with the signal at $\delta = 4.72$ ppm (H-7), which, in turn, coupled with the signal at $\delta = 4.25$ ppm (H-8).

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[25] The ten low-quality torsional parameters are: two Lp-O3-C0*00 [for the Lp−O(sp3)−C(sp2)=O(sp2) torsion, ester group], two H1-C2-C3-O3 [for the H−C(sp2)−C(sp3)−O(sp3) torsion, allylic ethers], two 00-C3-O3-00 [for the C(sp2)−C(sp3)−O(sp3)−C(sp2) torsion, allylic phenyl ethers], four Lp-O3-C0*00 [for the Lp−O(sp3)−C(sp2)=C(sp2) torsion, phenyl ethers].

[26] The six low-quality torsional parameters are: two Lp-O3-C0*00 [for the Lp−O(sp3)−C(sp2)=O(sp2) torsion, ester group], one 00*C2=C2*00 [for the (O=)C−CH=CH−C(=O) torsion, enedione], two 00-C2-C3-00 [for the O(sp3)−C(sp3)−C(sp2)−C(sp2) torsion], one C0-C3-O3-C2 [for the (O=)C−C(sp3)−O(sp3)−C(=O) torsion].

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Received: June 29, 2005
Published online: September 20, 2005

