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Synthesis of a 10-membered ring with eleutheside functionality by Nozaki–Hiyama–Kishi coupling

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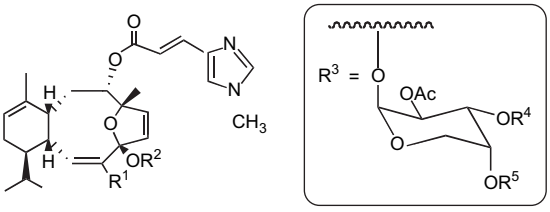
Dedicated to Professor Miguel Yus Astiz (University of Alicante, Spain) on occasion of his 60th anniversary

Abstract—The synthesis of a medium-sized unit of 15-seco-eleutheside analogue **3** has been achieved by the $NiCl_2/CrCl_2$-mediated intramolecular coupling of iodoaldehyde **8** with excellent yields. An important issue in our reported route to **3** involved a pyranose/furanose rearrangement, which opened the tetrahydrofuran ring on to the target.

1. Introduction

Mediterranean stoloniferan corals like *Sarcodictyon roseum* and Australian soft corals belonging to the *Eleutherobia* species are a rich source of oxacyclic diterpenes[1] like sarcodictyins **1**[2,3] and eleutherobin **2**[4,5] (Fig. 1).



1a: Sarcodictyin A : R^1= COOMe; R^2= H
1b: Sarcodictyin B : R^1= COOEt; R^2= H
2: Eleutherobin : R^1= CH_2R^3; R^2= Me; R^4= R^5= H

Figure 1.

These diterpenoids have in common the oxatricyclic ring system of the 4,7-oxaeunicellane skeleton, made of fused oxacyclononane and dihydrofurane units containing six stereogenic centres, three of them inside the medium-size oxacyclic ring. It has been shown that eleutherobin and sarcodictyins induce tubulin polymerization and stabilization of microtubules, causing mitotic arrest.[6] They exhibit potent activity against a range of human breast, renal, ovarian and lung cancer cell lines with a mean cytotoxicity (IC_{50} 10–15 nM) that was at least 100 times greater than that exhibited by taxol or the epothilones and have thus been included within the second generation of microtubule-stabilizing antimitotic agents.[7,8]

The scarce availability of these diterpenes from natural sources makes their total syntheses crucial for further biological investigations. To date, sarcodictyins have been synthesized successfully by Nicolaou et al.,[9] while eleutherobin has been synthesized by the groups of Nicolaou[10] and Danishefsky.[11] The synthesis of several key intermediates in the preparation of eleutherobin,[12–16] in addition to several approaches to the natural eleuthesides, and their analogues has also been described.[17]

As a part of our ongoing programme aimed at simplified eleutherobin analogues with improved synthetic accessibility although retaining microtubule-stabilizing properties, we described a brief and efficient synthesis of the eleutherobin aromatic analogue **3**.[18] The key step of our synthetic work was an intramolecular Nozaki–Hiyama–Kishi coupling to the iodoaldehyde **8** promoted by the Ni/Cr couple (Fig. 2). We now wish to report a full account of our synthetic strategy including interesting aspects concerning the intramolecular

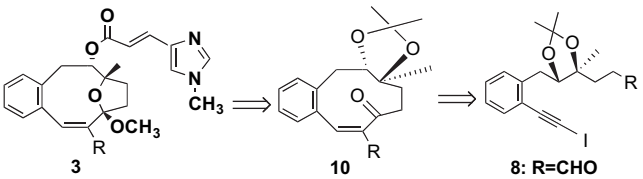


Figure 2.

Keywords: Eleuthesides; Eleutherobin; Nozaki–Hiyama–Kishi.
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cyclization of a ketodiol precursor. An important issue in our reported route to **3** involved a pyranose/furanose rearrangement, which opened the tetrahydrofuran ring on the target.

2. Results and discussion

In the course of our studies directed towards the synthesis of eleuthesides, we have developed a synthetic model based on an intramolecular cyclization leading to a 10-membered ring eleutheside analogue **3** of the fused oxacyclononane–tetrahydrofurane system very similar to the rigid oxygen-bridged bicyclo[8.4.0]tetradecatriene skeleton present in the antimitotic diterpenes **1** and **2**.

Planning the access to the 10-membered ring through a Nozaki–Kishi–Hiyama coupling,[19] we considered the preparation of the iodoaldehyde **8** as a key intermediate of our synthetic strategy. Preparation of **8** required application of a four-step sequence to the acetonide **4**, previously prepared by our group starting from *o*-bromophenetyl alcohol (Scheme 1).[20]

Reduction of the ester with diisobutylaluminium hydride in toluene at 0 °C led to the bromo alcohol **5** with excellent yield. Intermediate **5** was converted into the iodoaldehyde **8** by several consecutive transformations, which include Stille coupling, desilylation, iodination and oxidation of the alcohol. The Pd-catalyzed cross-coupling reaction of the bromo alcohol **5** with [(trimethylsilyl)ethynyl]tributyl stannane[21] allowed us to isolate the trimethylsilylacetylene **6**, with 93% yield under conditions described by Stille.[22] Other attempts to obtain **6** by Sonogashira–Hagihara coupling[23] through treatment of bromo derivative **5** with trimethylsilylacetylene and triethylamine, under the catalytic effect of $(Et_3P)_2PdCl_2$ in the presence of copper(I) iodide, led to the recovery of the starting material. The substitution of the silyl group by iodine was successfully accomplished by reaction with silver nitrate and *N*-iodosuccinimide. Fractionation of the reaction product by flash chromatography led to the isolation of **7** with 75% yield.[24]

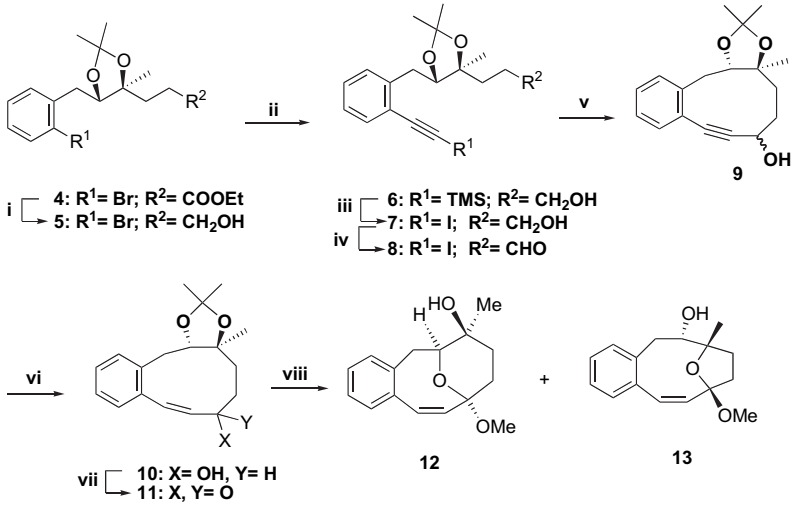
Alternative transformation of **6** into **7** by removal of the TMS protecting group by treatment of **6** with silver nitrate and potassium cyanide, followed by treatment of the acetylene intermediate with iodine and morpholine in benzene at room temperature, afforded the iodoacetylene **7** with lower yields (58%).[25] Finally, Dess–Martin periodinane oxidation of the acetylenic iodoalcohol **7** led to the precursor iodoaldehyde **8** with excellent yield (98%).

The crucial step of our strategy, the cyclization of **8** promoted by $CrCl_2$ and $NiCl_2$ (Nozaki–Hiyama–Kishi coupling[26]) proceeded smoothly, affording the 10-membered acetylenic alcohol **9** with 85% yield.

Transformation of the cycloalkynol **9** into the α,β-unsaturated ketone **11** was achieved by hydrogenation with Pd on $BaSO_4$ and quinoline followed by Dess–Martin oxidation with 88% overall yield. The use of Pd on $CaCO_3$ poisoned either with lead or with quinoline led to recovery of the starting material, while oxidation of the intermediate allylic alcohol with manganese dioxide afforded the unsaturated ketone **11** with somewhat lower yields (60%).

Treatment of **11** with *p*-toluenesulfonic acid in methanol at room temperature led to a mixture of two tricyclic acetals **12** and **13** with 22% and 45% yields, respectively (Scheme 1). The minor compound of the mixture, the pyrane **12**, was crystalline and the structural assignment was achieved by X-ray analysis (Fig. 3a).[27] When the cyclization was promoted by treatment of **11** with PPTS in refluxing methanol, the furan derivative **13** was the only compound, which was isolated from the reaction mixture (85% yield after flash chromatography). The structural assignment of **13** was based mainly on NOE correlations and NOESY experiments reported earlier.[18]

Structural correlation between **12** and **13** was made by hydrolysis of the acetal moiety followed by acetylation. Thus, simple exposure of **12** to the action of catalytic (1%) HCl in dioxane at room temperature led directly to **14**



Scheme 1. (i) DIBALH, toluene, 0 °C, 90%; (ii) $Bu_3SnCCTMS$, $Pd(PPh_3)_4$, toluene, reflux, 93%; (iii) NIS, $AgNO_3$, DMF, 75%; (iv) Dess–Martin, 98%; (v) $CrCl_2$, $NiCl_2$, THF, 85%; (vi) Pd/$BaSO_4$, quinoline, 90%; (vii) Dess–Martin, 98%; (viii) PPTS, CH_3OH, rt, (**12**/**13**=1:2; 67%) or PPTS, CH_3OH, reflux (**13**, 85%).

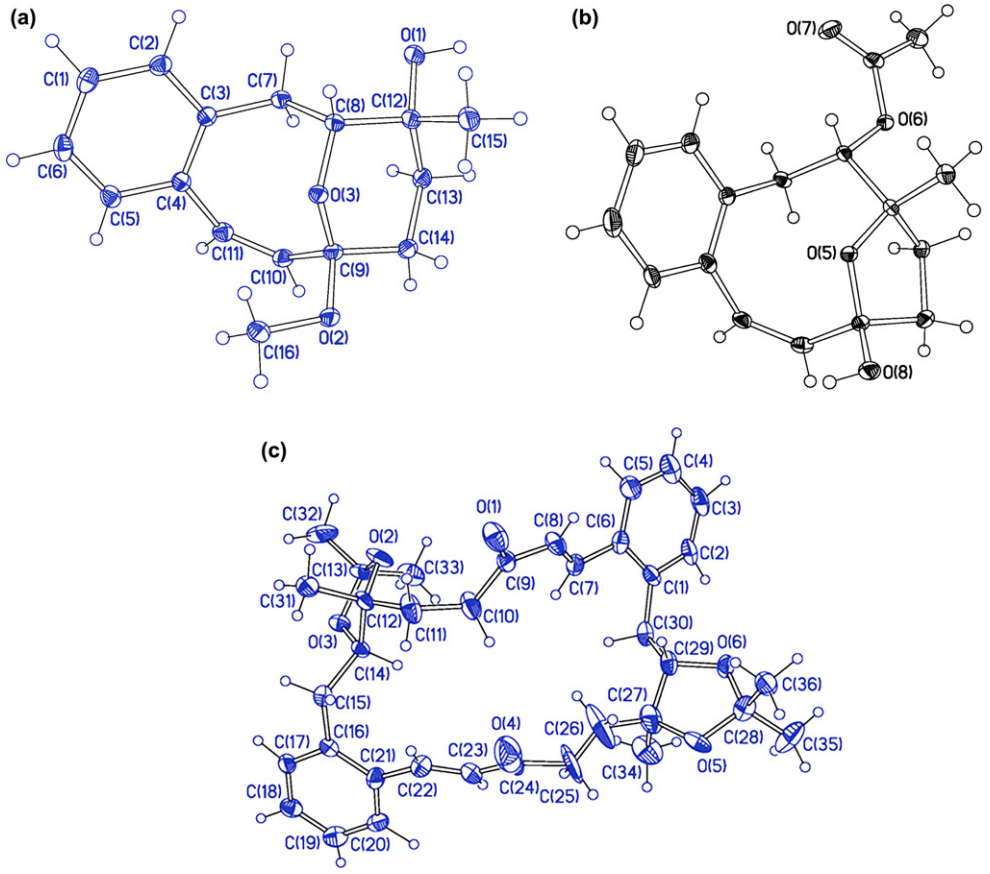
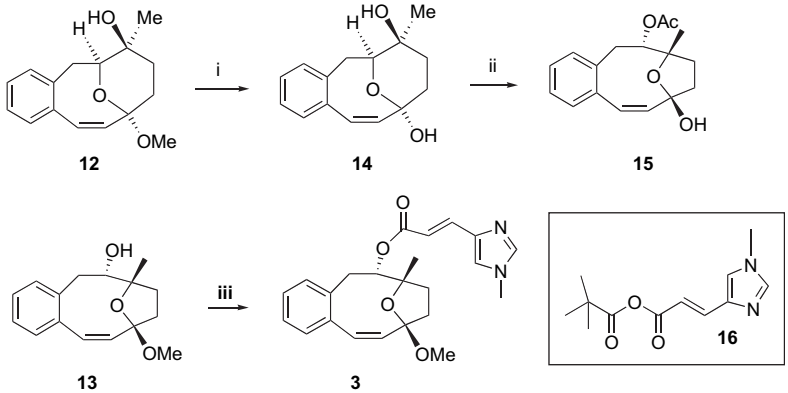


Figure 3. X-ray of (a) **12**, (b) **15** and (c) **21**. Displacement ellipsoids are drawn at the 50% probability label.

in excellent yields (Scheme 2). Then, the reaction of **14** with acetic anhydride and dimethylaminopyridine in dichloromethane at room temperature led to the acetate **15** with 80% yield. We took advantage of the fact that the masked secondary alcohol at C8 (eleutherobin numbering) could be selectively acetylated. This paved the way for cyclization of the tertiary alcohol into the carbonyl group of the enone of the open form, leading to the formation of **15**. The X-ray analysis of acetate **15** allowed us to ensure the definitive structural assignment of the final product of this sequence (Fig. 3b). This pyranose to furanose isomerization is in fact mediated by an 'anomeric' hydroxy function and has been previously observed by Danishefsky in his pioneering work on the synthesis of eleutherobin.[11]

The formation of the hydroxy pyrane **12** during the course of the acetonide deprotection reaction induced us to undertake computational studies in order to find out the relative stability of compounds **12** and **13**. After a conformational search performed with MM2 when the solvent effect was considered, the lower energy conformer of **12** is 5.76 kJ/mol less stable than that of **13**.



Scheme 2. (i) (1%) HCl, dioxane, rt, 77%; (ii) Ac_2O, Py, DMAP, CH_2Cl_2, 80%; (iii) **16**, CH_2Cl_2, Et_3N, DMAP, 85%.

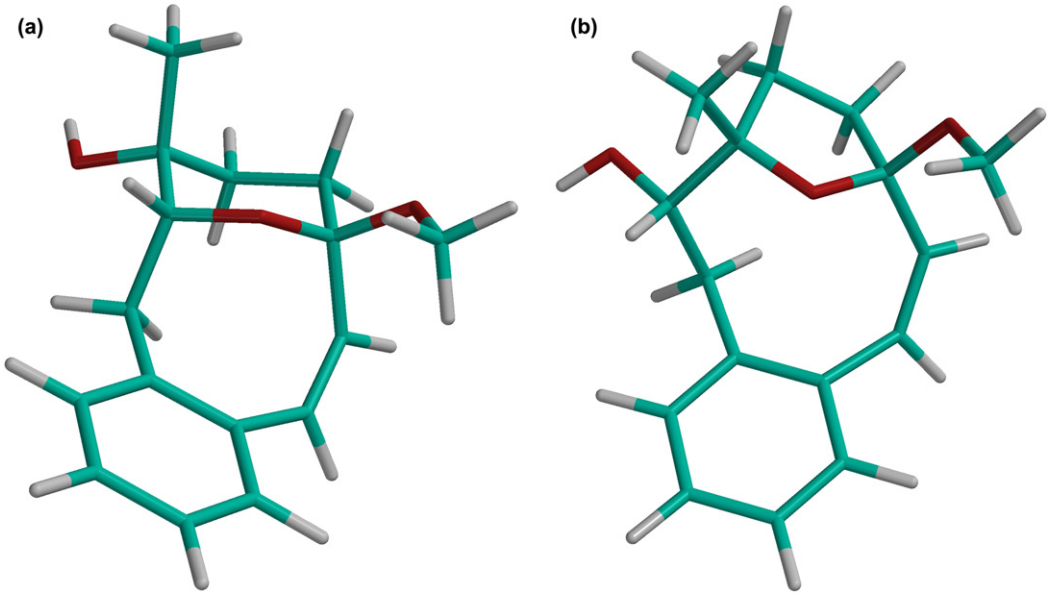


Figure 4. Lower energy conformer of compounds (a) **12** and (b) **13**.

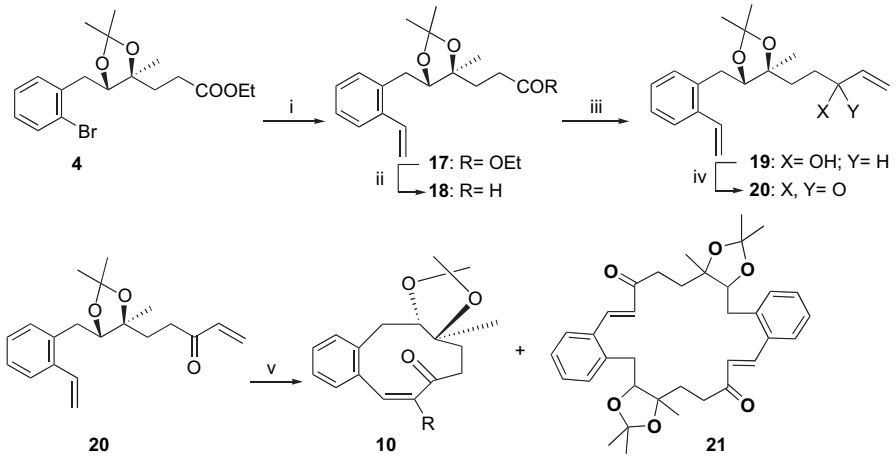
Ab initio studies at the HF/6-311G* level and Density Functional Theory (DFT) with the standard B3LYP/6-311G* performed on both global minima are in agreement with the results obtained by MM2 with a higher relative stability of **13** with respect to **12** by 11.53 kJ/mol (HF) and 12.58 kJ/mol (DFT).

The minimum energy conformers calculated, shown in Figure 4 are in excellent agreement with those found experimentally according to the NMR and X-ray diffraction data, which certainly validates the theoretical studies.

The coupling reaction of the furan derivative **13** with the mixed anhydride **16** led to the formation of the target analogue **3** with excellent yield (87%).

An alternative route to the preparation of the key compound, the α,β-unsaturated ketone **11**, was developed by ruthenium-promoted RCM of the bis olefin **20** (Scheme 3). The Pd-catalyzed coupling reaction of the bromoester **4** with tributylvinyltin in refluxing toluene afforded the arylvinyl derivative **17** with 95% yield. Then, the ester was further reduced by treatment with diisobutylaluminium hydride in toluene at −78 °C to afford the carboxaldehyde **18** in 98% yield. The vinylmagnesium bromide addition to the aldehyde **18** in THF at room temperature led to the allylic alcohol **19** as a (1:1) mixture of diastereomers with 70% yield. Dess–Martin periodinane oxidation of the allylic alcohol **19** in dichloromethane at room temperature afforded the α,β-unsaturated ketone **20** in quantitative yield.

The bis olefin **20** was subjected to RCM using a variety of catalysts. After a number of attempts, the recently developed Nolan and Grubbs' catalyst[28] gave the desired ring-closed product **10** in only 20% yield. The reaction only took place by the addition of a catalytic amount of $Ti[OCH(CH_3)_2]_4$ to increase the reactivity of the enone moiety. The major component of the reaction mixture, however,



Scheme 3. (i) $Bu_3SnCH{=}CH_2$, $Pd(PPh_3)_4$, toluene, 95%; (ii) DIBALH, toluene, −78 °C, 96%; (iii) $CH_2{=}CHMgBr$, THF, rt, 70%; (iv) Dess–Martin, 95%; (v) cat. $Ti(O^iPr)_4$, CH_2Cl_2, Ru(II) Nolan–Grubbs cat., reflux, 15 h, 75%.

was the dimer **21**, which was isolated in 55% yield. The trans configuration of the two acetonides in **21** was unambiguously demonstrated by X-ray analysis of the product (Fig. 3c).

3. Conclusion

The Cr/Ni-mediated intramolecular coupling of iodoaldehyde **8** and the RCM of the bis olefin **20** opened the access to the medium-sized bicyclic system present in the phenylcyclononane target skeleton of eleutherobin analogue **3**. Transformation of the ester **4** into the eleutheside-like tricyclic derivative **3** was accomplished by application of a 10-step sequence with 28% yield.

4. Experimental

4.1. General experimental methods

Melting points are uncorrected. ^{1}H NMR spectra were measured at either 200 or 400 MHz and ^{13}C NMR were measured at 50 or 100 MHz in $CDCl_3$ and referenced to TMS (^{1}H) or solvent (^{13}C), except where noted otherwise. IR spectra were recorded for neat samples on NaCl plates, unless otherwise noted. Standard mass spectrometry data were acquired by using GC–MS system in EI mode with the maximum *m*/*z* range of 600. Tetrahydrofuran (THF) was purified by distillation from sodium and benzophenone ketyl and degassed before use. Dimethylformamide (DMF) was dried over CaH_2, distilled under reduced pressure and degassed before use. Acetonitrile is fractionally distilled after refluxing over CaH_2. All reactions were conducted under a positive pressure of argon, utilizing standard bench-top techniques for handling of air-sensitive materials. Chromatographic separations were carried out under pressure on silica gel using flash column techniques.[9] R_f values refer to TLC carried out on 0.25 mm silica gel plates with the same eluent as that indicated for the column chromatography unless otherwise noted. Yields reported are for chromatographically pure isolated products unless mentioned otherwise. Anhydrous $CrCl_2$ and $NiCl_2$ were purchased from Aldrich and Strem Chemicals and were used without purification.

4.2. Methyl 3-((4*SR*,5*SR*)-5-(2-bromobenzyl)-2,2,4-trimethyl-1,3-dioxolan-4-yl)propanoate 4

2,2-Dimethoxypropane (5.4 mL, 43 mmol) and PPTS (15 mg) were added to a solution of diol **3** (4.9 g, 14.5 mmol) in dry dichloromethane (15 mL). The reaction mixture was stirred for 6 h at room temperature under argon atmosphere. Then the organic solution was washed with $NaHCO_3$ (10%) and brine. The combined layers were dried ($NaSO_4$) and the solvent evaporated at reduced pressure to afford a crude product (6.5 g), which was chromatographed on silica gel. Elution with hexanes/ethyl acetate (8:2) afforded **4** (6.1 g, 96%) as a colourless oil. R_f 0.45 (hexanes/ethyl acetate 1:1); IR (film) ν: 2984, 1170, 1437, 1375, 1217, 1092 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 1.13 (s, 3H); 1.18 (s, 3H); 1.26 (t, J=7 Hz, 3H); 1.35 (s, 3H); 1.83 (m, 2H); 2.41 (m, 2H); 2.83 (m, 2H); 3.98 (dd, J_1=10 Hz, J_2=2 Hz, 1H); 4.11 (q, J=7 Hz, 2H); 7.0–7.4 (m, 4H). ^{13}C NMR ($CDCl_3$) δ: 21.6 (q); 27.0 (q); 28.8 (q); 29.1 (t); 33.5 (t); 36.1 (t); 51.8 (q); 80.5 (d); 81.6 (s); 107.4 (s); 124.0 (s); 127.7 (d); 128.4 (d); 131.5 (d); 132.9 (d); 138.1 (s); 174.2 (c) ppm.

4.3. 3-((4*SR*,5*SR*)-5-(2-Bromobenzyl)-2,2,4-trimethyl-1,3-dioxolan-4-yl)propan-1-ol 5

To a solution of the ester **4** (100 mg, 0.27 mmol) in diethyl ether (2 mL), was added dropwise 1 mL of 1 M solution of DIBALH in toluene. The reaction mixture was stirred for 2.5 h at room temperature. Then, a saturated solution of sodium and potassium tartrate (5 mL) was added and the reaction mixture was stirred for 1 h. The reaction mixture was extracted with ethyl acetate and worked up as usually to afford after the evaporation of the solvent a crude product (120 mg), which was fractionated by flash chromatography. Elution with hexanes/ethyl acetate (7:3) afforded alcohol **5** (83 mg, 90%) as a solid, mp 52–54 °C; IR ($CHCl_3$) ν: 3414, 2984, 1375, 1217, 1028, 748 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.22 (s, 3H); 1.27 (s, 3H); 1.53 (s, 3H); 1.5–1.8 (m, 4H); 2.63 (dd, J_1=14 Hz, J_2=9 Hz, 1H); 2.90 (dd, J_1=14 Hz, J_2=3 Hz, 1H); 3.61 (t, J=5 Hz, 1H); 4.03 (dd, J_1=9 Hz, J_2=3 Hz, 1H); 7.1–7.5 (m, 4H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$) δ: 21.1 (q); 26.8 (q); 27.0 (t); 28.5 (q); 35.4 (t); 35.9 (t); 62.9 (t); 80.9 (d); 82.1 (s); 107.0 (s); 124.4 (s); 127.3 (d); 128.0 (d); 131.7 (d); 132.6 (d); 137.9 (s) ppm. MS (EI) (*m*/*z*) (%): 327 (M^+−15, 10), 267 (15), 171 (15), 115 (40), 84 (100), 69 (35).

4.4. 3-((4*SR*,5*SR*)-5-(2-(2-(Trimethylsilyl)ethynyl)benzyl)-2,2,4-trimethyl-1,3-dioxolan-4-yl)propan-1-ol 6

To a solution of **5** (0.362 g, 1.05 mmol) in 10 mL of dry, freshly distilled and deoxygenated toluene, were sequentially added [(trimethylsilyl)ethynyl]tributyl stannane (0.5 g, 1.37 mmol) and tetrakis triphenylphosphine Pd(0) (47 mg, 0.04 mmol). The reaction mixture was stirred for 5 h at reflux under argon atmosphere. Then a solution 5 N KF (5 mL) was added and the reaction mixture was stirred for 15 h at room temperature. Then the reaction mixture was filtered and extracted with diethyl ether; the combined organic layers were washed with brine and dried with Na_2SO_4. Evaporation of the solvent afforded a residue, which was fractionated by flash chromatography. Elution with hexanes/ethyl acetate (9:1) afforded **6** (0.264 g, 69%) as a colourless oil. R_f 0.45 (hexanes/ethyl acetate 8:2); IR (film) ν: 3447, 2957, 1373, 1250, 1049, 760 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 0.23 (s, 9H); 1.22 (s, 3H); 1.28 (s, 3H); 1.43 (s, 3H); 1.3–1.7 (m, 4H); 2.98 (m, 2H); 3.56 (m, 2H); 4.09 (dd, J_1=9 Hz, J_2=3 Hz, 1H); 7.1–7.5 (m, 4H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$) δ: 0.08 (3q); 21.0 (q); 26.9 (q); 27.1 (t); 28.6 (q); 34.1 (t); 35.7 (t); 62.9 (t); 81.9 (d); 82.1 (s); 98.4 (s); 103.7 (s); 106.9 (s); 122.8 (s); 126.2 (d); 128.5 (d); 129.5 (d); 132.6 (d); 140.5 (s) ppm. MS (EI) (*m*/*z*) (%): 360 (M^+, 10%), 345 (15), 269 (75), 243 (15), 212 (20), 188 (100), 153 (25), 115 (65), 73 (25).

4.5. 3-((4*SR*,5*SR*)-5-(2-(2-Iodoethynyl)benzyl)-2,2,4-trimethyl-1,3-dioxolan-4-yl)propan-1-ol 7

To a solution of **6** (0.262 g, 0.73 mmol) in DMF (5 mL) were sequentially added *N*-iodosuccinimide (0.246 g, 1.09 mmol)

and silver nitrate (0.012 g, 0.07 mmol). The reaction mixture was stirred for 24 h in the dark at room temperature. Then, water (5 mL) was added. The reaction mixture was extracted with ethyl acetate, the combined organic layers were washed with brine and dried over Na_2SO_4. Evaporation of the solvent afforded a residue, which was fractionated by flash chromatography on silica gel. Elution with hexanes/ethyl acetate (8:2) and evaporation of the solvent afforded **7** (0.165 g, 55%) as a yellow oil; IR (film) ν: 3420, 2936, 1375, 1217, 1096, 909, 733 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ: 1.22 (s, 3H); 1.26 (s, 3H); 1.44 (s, 3H); 1.5–1.8 (m, 4H); 2.88 (dd, J_1=14 Hz, J_2=9 Hz, 1H); 2.97 (dd, J_1=14 Hz, J_2=3 Hz, 1H); 3.65 (t, J=5 Hz, 2H); 4.03 (dd, J_1=9 Hz, J_2=3 Hz, 1H); 7.1–7.5 (m, 4H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$) δ: 9.9 (q); 21.0 (q); 26.9 (q); 27.2 (t); 28.6 (q); 34.5 (t); 35.8 (t); 63.2 (t); 82.1 (d); 82.1 (s); 93.0 (s); 107.0 (s); 122.8 (s); 126.2 (d); 128.9 (d); 129.8 (d); 133.0 (d); 141.6 (s) ppm. MS (EI) (*m*/*z*) (%): 399 (M^+-15, 20), 241 (70), 181 (25), 115 (100).

4.6. 3-((4*SR*,5*SR*)-5-(2-(2-Iodoethynyl)benzyl)-2,2,4-trimethyl-1,3-dioxolan-4-yl)propanal 8

To a solution of **7** (0.145 g, 0.35 mmol) in dichloromethane (3 mL), the Dess–Martin periodinane (0.24 g, 0.56 mmol) was added. The reaction mixture was stirred for 8 h at room temperature; then, solutions of $NaHCO_3$ (10%) (4 mL) and $Na_2S_2O_3$ (10%) (2 mL) were added. The reaction mixture was extracted with diethyl ether, and the combined organic layers were washed with brine and dried over Na_2SO_4. Evaporation of the solvent afforded **8** (0.125 g, 87%) as a colourless oil. R_f 0.55 (hexanes/ether 9:1); IR (film) ν: 2930, 1723, 1375, 1217, 1098, 758, 665 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ: 1.15 (s, 3H); 1.17 (s, 3H); 1.36 (s, 3H); 1.8–2.0 (m, 2H); 2.52 (t, J=7 Hz, 2H); 2.8 (dd, J_1=14 Hz, J_2=9 Hz, 1H); 2.9 (dd, J_1=14 Hz, J_2=3 Hz, 1H); 3.9 (dd, J_1=9 Hz, J_2=3 Hz, 1H); 7.0–7.4 (m, 4H); 9.73 (s, 1H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$) δ: 10.2 (s); 21.9 (q); 27.0 (q); 28.8 (q); 30.9 (t); 34.7 (t); 39.1 (t); 81.4 (d); 81.5 (s); 93.2 (s); 107.5 (s); 123.0 (s); 126.6 (d); 129.2 (d); 130.1 (d); 133.3 (d); 141.6 (s); 202.4 (d) ppm. MS (EI) (*m*/*z*) (%): 412 (M^+, 2), 397 (10), 254 (15), 241 (35), 199 (20), 171 (55), 127 (50), 113 (100), 69 (30).

4.7. Alkynol 9

In a 10 mL flask were placed $NiCl_2$ (12 mg, 0.09 mmol), $CrCl_2$ (126 mg, 1.0 mmol), 4 Å molecular sieves (5 mg) and dry, freshly distilled and deoxygenated THF (2.5 mL). To this suspension a solution of the iodoaldehyde **8** (64 mg, 0.15 mmol) in dry, freshly distilled and deoxygenated THF (1.5 mL) was added dropwise. The reaction mixture was stirred for 1 h at room temperature. Then, water (2 mL) was added, the reaction mixture was extracted with diethyl ether, the combined organic layers were washed with brine and dried over Na_2SO_4 to afford a crude residue (57 mg) after evaporation of the solvent. The crude product was fractionated by flash chromatography. Elution with hexanes/ethyl acetate (1:1) and evaporation of the solvent afforded the cyclic alkynol **9** (37 mg, 84%) as a solid, mp 182–184 °C (diisopropyl ether); IR (KBr) ν: 3441, 2928, 1743, 1025, 761 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 1.24 (s, 3H); 1.26 (s, 3H); 1.47 (s, 3H); 1.93–2.05 (m, 4H); 2.52 (dd, J_1=16 Hz, J_2=8 Hz, 1H); 3.12 (d, J=12 Hz, 1H); 4.50 (d, J=8 Hz, 1H); 4.81 (m, 1H); 7.22–7.36 (m, 4H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ: 22.6 (q); 26.9 (q); 28.4 (q); 30.0 (t); 30.6 (t); 31.3 (t); 35.8 (t); 62.6 (d); 77.1 (d); 82.3 (s); 84.5 (s); 98.4 (s); 106.3 (s); 120.1 (s); 126.6 (d); 129.2 (d); 129.8 (d); 130.6 (d); 143.7 (s) ppm. MS (FAB) (*m*/*z*) (%): 287 (M^++1), 268 (4), 211 (10), 69 (64), 55 (100).

4.8. Alkenol 10

A solution of **9** (0.115 g, 0.4 mmol) in ethanol (5 mL) was added dropwise to a suspension of $Pd(BaSO_4)$ (0.44 g, 5% Pd) in ethanol (2 mL). The reaction mixture was stirred for 24 h at room temperature under hydrogen atmosphere. The reaction mixture was filtered and the solvent evaporated to give a residue, which is purified by flash silica gel. Elution with hexanes/ethyl acetate (85:15) afforded **10** (0.1 g, 90%) as a colourless oil. R_f 0.55 (hexane/ethyl acetate 9:1); IR (film) ν: 3434, 2938, 1377, 1217, 1017, 756 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ: 1.10 (s, 3H); 1.23 (s, 3H); 1.44 (s, 3H); 1.6–1.9 (m, 4H); 2.71 (m, 2H); 3.91 (m, 1H); 4.15 (m, 1H); 5.76 (dd, J_1=10 Hz, J_2=1 Hz, 1H); 6.48 (d, J=10 Hz, 1H); 7.1–7.4 (m, 4H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$) δ: 20.0 (q); 26.8 (q); 28.4 (q); 32.0 (t); 32.2 (t); 35.1 (t); 68.6 (d); 82.7 (s); 83.9 (d); 106.5 (s); 126.0 (d); 127.7 (d); 128.3 (d); 129.0 (d); 129.8 (d); 134.5 (d); 134.9 (s); 138.4 (s) ppm. MS (EI) (*m*/*z*) (%): 288 (M^+, 5), 273 (20), 195 (35), 154 (40), 129 (100), 115 (60), 91 (30).

4.9. Enone 11

The Dess–Martin periodinane (0.135 mg, 0.32 mmol) was added to a solution of **10** (0.080 g, 0.27 mmol) in dichloromethane (5 mL). The reaction mixture was stirred for 5 h at room temperature. Then 0.1 M $Na_2S_2O_3$ (1.5 mL) and 10% $NaHCO_3$ (3 mL) were added. The reaction mixture was filtered and extracted with diethyl ether. The combined organic layers were washed with brine, dried over Na_2SO_4 and the solvent evaporated to afford **11** (78 mg, 99%), mp 131–133 °C (hexane) R_f 0.65 (hexanes/ethyl acetate 9:1); IR ($CHCl_3$) ν: 2984, 2936, 1694, 1443, 1377, 1074, 772 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 1.18 (s, 3H); 1.31 (s, 3H); 1.48 (s, 3H); 1.85 (m, 1H); 2.25 (t, 1H); 2.44 (ddd, J_1=12 Hz, J_2=8 Hz, J_3=2.5 Hz, 2H); 2.69 (d, J=3.5 Hz, 2H); 3.69 (t, J=3.5 Hz, 1H); 6.45 (d, J=12 Hz, 1H); 6.78 (d, J=12 Hz, 1H); 7.17–7.43 (m, 4H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ: 19.6 (q); 26.7 (q); 28.5 (q); 31.8 (t); 33.0 (t); 37.1 (t); 82.7 (d); 83.0 (s); 106.5 (s); 126.3 (d); 128.1 (d); 128.2 (d); 130.1 (d); 133.1 (d); 133.2 (d); 134.3 (s); 136.5 (s); 203.4 (s) ppm. MS (EI) (*m*/*z*) (%): 286 (M^+, 5), 271 (25), 211 (45), 154 (40), 129 (75), 99 (55), 69 (100).

4.10. Pyrane 12 and tetrahydrofurane 13

p-Toluenesulfonic acid monohydrate (25 mg, 0.13 mmol) was added to a solution of **11** (76 mg, 0.26 mmol) in methanol (2 mL). The reaction mixture was stirred for 10 h at room temperature. Then saturated $NaHCO_3$ (2 mL) was added, the methanol evaporated and the aqueous layer was extracted with ethyl acetate. The residue was fractionated

by flash chromatography on silica gel. Elution with hexane/ethyl acetate (7:3) afforded **12** (15 mg, 22%) and **13** (30 mg, 44%).

Compound **12**: R_f 0.65 (hexanes/ethyl acetate 1:1), mp 166–168 °C (hexane); IR ($CHCl_3$) ν: 3464, 2932, 1709, 1449, 1262, 1069, 758 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 1.52 (s, 3H); 1.65 (ddt, J_1=13 Hz, J_2=4 Hz, J_3=1.2 Hz, 1H); 1.95 (m, 2H); 2.15 (m, 1H); 2.85 (dd, J_1=12.8 Hz, J_2=4.8 Hz, 1H); 3.0 (s, 3H); 3.19 (t, J=13 Hz, 1H); 3.65 (dd, J_1=12.8 Hz, J_2=4.8 Hz, 1H); 5.38 (d, J=12.5 Hz, 1H); 6.73 (d, J=12.5 Hz, 1H); 7.21–7.26 (m, 4H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ: 27.4 (q); 30.8 (t); 33.7 (t); 35.6 (t); 49.5 (q); 70.7 (s); 81.5 (d); 98.8 (s); 126.0 (d); 127.2 (d); 127.8 (d); 128.6 (d); 132.2 (d); 132.4 (d); 136.3 (s); 138.2 (s) ppm. MS (EI) (*m*/*z*) (%): 260 (M^+, 10), 173 (10), 159 (100), 129 (25), 115 (25), 91 (10), 81 (15), 69 (20). MS (HREI) calcd for $C_{16}H_{20}O_3$: (M^+) 260.1412. Found: 260.1418.

Compound **13**: R_f 0.60 (hexanes/ethyl acetate 1:1); IR ($CHCl_3$) ν: 3462, 2974, 1458, 1217, 1053, 758 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 1.31 (s, 3H); 1.70 (m, 1H); 2.18 (m, 2H); 2.31 (m, 1H); 2.59 (d, J=13 Hz, 1H); 3.09 (s, 3H); 3.30 (t, J=12.5 Hz, 1H); 3.94 (d, J=12 Hz, 1H); 5.57 (d, J=12.5 Hz, 1H); 6.67 (d, J=12.5 Hz, 1H); 7.01–7.24 (m, 4H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$) δ: 27.2 (q); 28.9 (t); 37.2 (t); 38.9 (t); 50.9 (q); 80.2 (d); 87.8 (s); 110.3 (s); 125.3 (d); 126.4 (d); 127.8 (d); 129.1 (d); 132.3 (d); 132.5 (d); 137.4 (s); 137.8 (s) ppm. MS (EI) (*m*/*z*) (%): 260 (M^+, 10), 242 (30), 184 (35), 159 (100), 115 (35), 99 (35), 77 (15). MS (HREI) calcd for $C_{16}H_{20}O_3$: (M^+) 260.1412. Found: 260.1391.

4.11. Molecular model calculations

Molecular modelling calculations were performed on a Octane 350 Silicon Graphics and a Macintosh RackMac3,1 PowerPC G5 computers. Compounds **12** and **13** were built using Macromodel v.5.5.[29] Conformational analysis of the two compounds was performed by a Monte Carlo random search[30] using up to 1000 steps. All freely rotating bonds were searched with MM2 minimization to a gradient of less than 0.001 kcal/mol. In order to reproduce the experimental conditions, calculations were performed considering chloroform as solvent. MacroModel uses a solvation model, which treats the solvent as an analytical continuum starting near the van der Waals surface of the solute (GB/SA).[31] The lower energy conformer of compounds **12** and **13** was adopted as the initial geometries for a full geometry optimization of the two compounds, which was performed using a molecular orbital ab initio method at the Hartree–Fock with the 6-31G* *basis set* and Density Functional Theory (DFT)[32] with the standard B3LYP/6-31+G* using the SPARTAN 04′ Macintosh program distributed by Wavefunction Inc. The models were considered as closed-shell systems (restricted calculations).

4.12. Pyrane hemiacetal 14

A solution of **12** (0.056 g, 0.2 mmol) in dioxane (10 mL) was placed in a 50 mL flask equipped with a magnetic bar; HCl (1%, 15 mL) was added and the reaction mixture was stirred for 15 h at room temperature. Water (15 mL) was added and the reaction mixture was extracted with ethyl acetate. The combined organic layers were washed with (10%) Na_2CO_3 and brine and dried over Na_2CO_3. Evaporation of the solvent afforded a residue, which was chromatographed on silica gel. Elution with hexanes/ethyl acetate (6:4) afforded **14** (40 mg, 77%) as a solid, mp 71–73 °C (hexane); IR ($CHCl_3$) ν: 3349, 2934, 1717, 1449, 1080, 758 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ: 1.55 (s, 3H); 1.63–2.16 (m, 4H); 2.86 (dd, J_1=13 Hz, J_2=4.7 Hz, 1H); 3.19 (t, J=13 Hz, 1H); 3.68 (dd, J_1=13 Hz, J_2=4.7 Hz, 1H); 5.71 (d, J=12.5 Hz, 1H); 6.48 (d, J=12.5 Hz, 1H); 7.21–7.32 (m, 4H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$) δ: 27.3 (q); 30.9 (t); 33.7 (t); 35.4 (t); 70.4 (s); 82.2 (d); 96.1 (s); 126.1 (d); 127.4 (d); 128.2 (d); 128.7 (d); 128.9 (d); 135.9 (d); 136.4 (s); 137.6 (s) ppm. MS (EI) (*m*/*z*) (%): 246 (M^+, 10), 228 (10), 145 (100), 129 (20), 115 (20), 99 (25), 83 (35), 69 (20).

4.13. Tetrahydrofurane hemiacetal 15

A solution of **14** (0.023 g, 0.09 mmol) in dichloromethane (5 mL) was placed in a 50 mL flask equipped with a magnetic bar. Acetic anhydride (0.014 mL, 0.15 mmol) and dimethylaminopyridine (0.020 g, 0.16 mmol) were added and the reaction mixture was stirred for 24 h at room temperature under nitrogen. Then reaction mixture was washed with (5%) citric acid, (10%) $NaHCO_3$ and brine. The organic phase was dried over Na_2SO_4 and the solvent evaporated to afford a residue, which was fractionated on silica gel. Elution with hexanes/diethyl ether (8:2) afforded **15** (0.021 g, 80%) as a solid, mp 179–181 (hexane); IR ($CHCl_3$) ν: 3482, 2930, 1734, 1456, 1373, 1244, 1030, 756 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 1.25 (s, 3H); 1.79 (m, 1H); 2.11 (s, 3H); 2.15–2.30 (m, 2H); 2.42 (m, 1H); 2.61 (d, J=13 Hz, 1H); 3.21 (dd, J_1=13 Hz, J_2=1.9 Hz, 1H); 4.98 (d, J=13 Hz, 1H); 5.84 (d, J=12.5 Hz, 1H); 6.48 (d, J=12.5 Hz, 1H); 7.01–7.50 (m, 4H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ: 21.3 (q); 27.3 (q); 30.6 (t); 35.2 (t); 37.8 (t); 81.2 (d); 86.2 (s); 107.3 (s); 125.7 (d); 127.0 (d); 127.9 (d); 129.7 (d); 129.8 (d); 134.4 (d); 136.4 (s); 137.1 (s); 170.4 (s) ppm. MS (EI) (*m*/*z*) (%): 288 (M^+, 10), 264 (15), 256 (15), 228 (100), 219 (45), 157 (25), 99 (100). MS (HREI) calcd for $C_{17}H_{20}O_4$: (M^+) 288.1351. Found: 288.1361.

4.14. Analogue 3

The alcohol **15** (0.115 g, 0.40 mmol) was added to a solution of the freshly prepared mixed anhydride **16** (1.65 g, 6.5 mmol), dimethylaminopyridine (0.160 g, 1.3 mmol) and triethylamine (1.25 mL) in dichloromethane (25 mL). The reaction mixture was stirred at room temperature for 48 h under argon atmosphere. The solvent was evaporated and the residue was chromatographed on silica gel. Elution with $CHCl_3$/MeOH (95:5) afforded **3** (0.130 g, 75%) as a colourless oil. R_f 0.65 (Cl_3CH/MeOH 98:2); IR ($CHCl_3$) ν: 2862, 1705, 1638, 1271, 1167, 1123, 754 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 1.21 (s, 3H); 1.95 (m, 2H); 2.22 (m, 2H); 2.71 (dd, J_1=13 Hz, J_2=5 Hz, 1H); 3.04 (s, 3H); 3.21 (t, J=13 Hz, 1H); 3.70 (s, 3H); 4.22 (dd, J_1=13 Hz, J_2=5 Hz, 1H); 5.36 (d, J=12.4 Hz, 1H); 6.54 (d, J=15.6 Hz, 1H); 6.71 (d, J=12.4 Hz, 1H); 7.08 (s, 1H);

7.16–7.22 (m, 4H); 7.48 (s, 1H); 7.51 (d, J=15.6 Hz, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ: 26.8 (q); 28.0 (t); 33.5 (q); 33.6 (t); 34.8 (t); 49.6 (q); 79.4 (d); 80.5 (s); 98.8 (s); 117.2 (d); 122.4 (d); 126.1 (d); 126.8 (d); 126.9 (d); 128.9 (d); 131.9 (d); 132.5 (d); 135.6 (d); 138.0 (s); 138.1 (s); 138.3 (s); 139.1 (d); 166.5 (s) ppm. MS (EI) (*m*/*z*) (%): 394 (M^+, 10), 369 (10), 266 (10), 207 (8), 166 (6), 135 (100), 108 (27), 57 (28).

4.15. Ethyl 3-((4*S*,5*S*)-5-(2-vinylbenzyl)-2,2,4-trimethyl-1,3-dioxolan-4-yl)propanoate 17

A solution of **4** (0.480 g, 1.39 mmol) in freshly distilled and deoxygenated toluene (12 mL) was placed in a 100 mL flask and tributylvinyltin (0.55 mL, 1.8 mmol), tetrakistriphenylphosphine Pd(0) (30 mg, 0.02 mmol) and 2,6-di-*tert*-butyl-4-methyl-phenol (5 mg) were successively added under nitrogen atmosphere. The reaction mixture was stirred for 5 h under reflux, then cooled to room temperature, aqueous 5 N KF (25 mL) was added and the reaction mixture was stirred overnight at the same temperature. The reaction was filtered and extracted with diethyl ether. The combined organic layers were washed with brine, dried over Na_2SO_4 and evaporated to give a residue, which was fractionated on silica gel. Elution with hexanes/ethyl acetate (95:5) afforded **17** (0.390 g, 95%) as a solid, mp 50–52 °C. R_f 0.55 (hexane/ethyl acetate 9:1). ^{1}H NMR (200 MHz, $CDCl_3$) δ: 0.92 (t, J=7 Hz, 3H); 1.26 (s, 3H); 1.29 (s, 3H); 1.43 (s, 3H); 1.64 (m, 2H); 2.41 (m, 2H); 2.60 (dd, J_1=14 Hz, J_2=4 Hz, 1H); 2.89 (dd, J_1=14 Hz, J_2=8 Hz, 1H); 3.99 (dd, J_1=8 Hz, J_2=4 Hz, 1H); 4.00 (q, J=7 Hz, 2H); 5.35 (d, J=11 Hz, 1H); 5.68 (d, J=17 Hz, 1H); 6.94 (dd, J_1=17 Hz, J_2=11 Hz, 1H); 7.2–7.5 (m, 4H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$) δ: 14.4 (q); 21.7 (q); 27.0 (q); 28.8 (q); 29.3 (t); 32.9 (t); 33.4 (t); 60.5 (t); 81.4 (d); 81.6 (s); 107.1 (s); 116.3 (t); 126.4 (d); 127.0 (d); 128.0 (d); 130.1 (d); 135.0 (d); 135.8 (s); 137.3 (s); 173.8 (s) ppm. MS (EI) (*m*/*z*) (%): 317 (M^+−15), 274 (10), 259 (15), 228 (10), 211 (20), 183 (10), 169 (20), 157 (100), 129 (75), 111 (70), 99 (45), 83 (40), 55 (50).

4.16. 3-((4*S*,5*S*)-5-(2-Vinylbenzyl)-2,2,4-trimethyl-1,3-dioxolan-4-yl)propanal 18

A solution of ester **17** (0.4 g, 1.2 mmol) in freshly distilled and deoxygenated toluene (10 mL) was placed in a 100 mL flask equipped with a magnetic stirrer. A 1 M diisobutylaluminium hydride solution in toluene (1.25 mL) was added dropwise at −78 °C and the reaction mixture was stirred for 1 h under argon at the same temperature. Then, a saturated solution of sodium and potassium tartrate (10 mL) was added and the reaction mixture was left to warm up to room temperature. The reaction mixture was extracted with ethyl acetate, the combined organic layers were washed with brine and dried over Na_2SO_4 to afford **18** (0.33 g, 96%) after evaporation of the solvent; IR (film) ν: 2984, 2934, 1724, 1375, 1217, 1098, 1024, 991, 916, 772 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.21 (s, 3H); 1.28 (s, 3H); 1.43 (s, 3H); 1.58–1.78 (m, 2H); 2.51 (t, J=7 Hz, 2H); 2.82 (dd, J_1=14 Hz, J_2=4 Hz, 1H, Ar-CH_2); 2.97 (dd, J_1=14 Hz, J_2=8 Hz, 1H, Ar-CH_2); 3.98 (dd, J_1=8 Hz, J_2=4 Hz, 1H); 5.36 (d, J=11 Hz, 1H); 5.60 (d, J=17 Hz, 1H); 6.94 (dd, J_1=17 Hz, J_2=11 Hz, 1H); 7.2–7.5 (m, 4H); 9.72 (s, 1H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$) δ: 21.6 (q); 26.7 (q); 28.5 (q); 30.5 (t); 32.7 (t); 38.6 (t); 81.2 (d); 81.3 (s); 107.0 (s); 116.0 (t); 126.1 (d); 126.9 (d); 127.8 (d); 129.9 (d); 134.8 (d); 135.4 (s); 137.0 (s); 201.8 (d) ppm. MS (EI) (*m*/*z*) (%): 288 (M^+, 2), 273 (10), 230 (10), 202 (10), 171 (20), 113 (100), 84 (20), 69 (55).

4.17. 5-((4*S*,5*S*)-5-(2-Vinylbenzyl)-2,2,4-trimethyl-1,3-dioxolan-4-yl)pent-1-en-3-ol 19

A solution of 1 M vinylmagnesium bromide (2.75 mL) in THF (16 mL) was added dropwise to a solution of **18** (0.67 g, 2.30 mmol) in THF (15 mL). The reaction mixture was stirred for 1 h at room temperature under argon atmosphere. Then, saturated NH_4Cl (15 mL) was added and the reaction mixture was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over Na_2SO_4 and the solvent evaporated to give a residue, which was fractionated on silica gel. Elution with hexanes/ethyl acetate (9:1) afforded **19** (0.43 g, 70%). R_f 0.55 (hexanes/ethyl acetate 8:2); IR (film) ν: 3447, 2984, 1375, 1217, 1096, 991, 920, 772 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.23 (s, 3H); 1.28 (s, 3H); 1.44 (s, 3H); 1.48–1.67 (m, 4H); 2.70 (dd, J_1=14 Hz, J_2=4 Hz, 1H); 2.91 (dd, J_1=14 Hz, J_2=8 Hz, 1H); 4.00 (m, 2H); 5.05 (d, J=11 Hz, 1H); 5.16 (d, J=17 Hz, 1H); 5.29 (d, J=11 Hz, 1H); 5.68 (d, J=17 Hz, 1H); 5.80 (m, 1H); 6.94 (dd, J_1=17 Hz, J_2=11 Hz, 1H); 7.2–7.5 (m, 4H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$) δ: 21.4 (q); 21.5 (q); 26.9 (q); 28.6 (q); 31.2 (t); 31.4 (t); 32.9 (t); 34.1 (t); 34.9 (t); 72.6 (d); 73.2 (d); 81.8 (d); 82.1 (s); 106.9 (s); 114.4 (t); 116.0 (t); 126.2 (d); 126.8 (d); 127.8 (d); 130.0 (d); 134.9 (d); 135.7 (s); 137.2 (s); 141.0 (d); 141.1 (d) ppm. MS (EI) (*m*/*z*) (%): 316 (M^+, 2), 301 (10), 258 (10), 173 (15), 141 (100), 117 (75), 95 (40).

4.18. 5-((4*S*,5*S*)-5-(2-Vinylbenzyl)-2,2,4-trimethyl-1,3-dioxolan-4-yl)pent-1-en-3-one 20

Dess–Martin periodinane (0.27 mg, 0.65 mmol) was added to a solution of **19** (0.171 g, 0.54 mmol) in dichloromethane (2 mL). The reaction mixture was stirred for 5 h at room temperature. Then 0.1 M $Na_2S_2O_3$ (3 mL) and 10% $NaHCO_3$ (5 mL) were added. The reaction mixture was filtered and extracted with diethyl ether. The combined organic layers were washed with brine, dried over Na_2SO_4 and the solvent evaporated to afford a residue, which was fractionated by flash chromatography on silica gel. Elution with hexane/ethyl acetate (8:2) afforded **20** (0.161 g, 95%) as a colourless oil. R_f 0.45 (hexanes/ethyl acetate 9:1); IR (film) ν: 2984, 2934, 1684, 1375, 1217, 1096, 991, 924, 772 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.22 (s, 3H); 1.26 (s, 3H); 1.44 (s, 3H); 1.6–1.9 (m, 2H); 2.71 (t, J=7.5 Hz, 2H); 2.81 (dd, J_1=14 Hz, J_2=4 Hz, 1H); 2.89 (dd, J_1=14 Hz, J_2=8 Hz, 1H); 3.96 (dd, J_1=8 Hz, J_2=4 Hz, 1H); 5.29 (d, J=11 Hz, 1H); 5.59 (d, J=17 Hz, 1H); 5.79 (dd, J_1=11 Hz, J_2=2 Hz, 1H); 6.15 (dd, J_1=17 Hz, J_2=11 Hz, 1H); 6.23 (d, J=17 Hz, 1H), 6.95 (dd, J_1=17 Hz, J_2=11 Hz, 1H); 7.2–7.5 (m, 4H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$) δ: 21.5 (q); 26.8 (q); 28.6 (q); 32.0 (t); 32.7 (t); 34.2 (t); 81.6 (d); 81.6 (s); 106.8 (s); 116.0 (t); 126.1 (d); 126.8 (d); 127.8 (d); 127.9 (t); 129.9 (d); 134.8 (d); 135.6 (s); 136.4 (d); 137.0 (s); 200.1 (s) ppm. MS (EI) (*m*/*z*) (%): 314 (M^+, 2),

299 (5), 256 (10), 197 (10), 173 (10), 139 (100), 117 (30), 91 (10), 77 (10).

4.19. Dimer 21

A solution of **20** (0.088 g, 0.28 mmol) in freshly distilled and deoxygenated dichloromethane (45 mL) was placed in a Schlenk flask. Then, titaniumtetraisopropoxide (0.084 mmol) and tricyclohexylphosphine [1,3-bis-(2,4,6-trimethyl phenyl)-4,5-dihydro-imidazol-2-ylidene](phenylmethylene)ruthenium(II) dichloride (0.023 g, 0.028 mmol) were added and the reaction mixture was heated to reflux under argon for 15 h. Then the reaction mixture was left to cool to room temperature, filtered and the solvent evaporated to give a residue, which was fractionated by flash chromatography on silica gel. Elution with hexanes/ethyl acetate (8:2) afforded **11** (0.016 g, 20%) and **21** (0.044 g, 55%) as a solid, mp 225–227 °C (hexane). R_f 0.45 (hexanes/ethyl acetate 9:1); IR (KBr) ν: 2977, 2933, 1614, 1375, 1217, 1093, 749 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 1.21 (s, 6H); 1.23 (s, 6H); 1.43 (s, 6H); 1.73 (m, 2H); 1.93 (m, 2H); 2.59 (m, 2H); 2.84 (m, 2H); 2.86 (dd, J_1=14 Hz, J_2=9 Hz, 2H); 3.03 (dd, J_1=14 Hz, J_2=3.5 Hz, 2H); 3.84 (dd, J_1=9 Hz, J_2=3.5 Hz, 1H); 6.70 (d, J=16 Hz, 2H); 7.27–7.36 (m, 6H); 7.50 (d, J=7 Hz, 2H); 7.84 (d, J=7 Hz, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ: 22.0 (q); 26.9 (q); 28.6 (q); 32.0 (t); 33.6 (t); 36.1 (t); 81.4 (d); 81.6 (s); 107.0 (s); 127.0 (d); 127.2 (d); 127.8 (d); 130.0 (d); 131.5 (d); 133.3 (s); 138.1 (s); 139.7 (d); 198.8 (s) ppm. MS (FAB) (*m*/*z*) (%): 573 (M^++1, 6), 457 (12), 221 (35).

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Supplementary data

Crystallographic data and structure refinements for compounds **12**, **15** and **21** can be found in the online version. Supplementary spectroscopic data associated with this article can be found in the online version, at doi:10.1016/j.tet.2007.08.099.

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