



Synthesis of an orthogonally protected polyhydroxylated cyclopentene from L-Sorbose

Title	Synthesis of an orthogonally protected polyhydroxylated cyclopentene from L-Sorbose
Author(s)	Lo Re, Daniele; Jones, Leigh F.; Giralt, Ernest; Murphy, Paul V.
Publication Date	2016-07-06
Publisher	Chemical Editorial Society (ACES) / Wiley

Synthesis of an orthogonally protected polyhydroxylated cyclopentene from L-sorboseDaniele Lo Re^{a*}, Leigh Jones^a, Ernest Giralt^{b,c} and Paul Murphy^{a*}Dedicated to M^a Teresa Plaza López-Espinosa on the occasion of her retirement ((optional))

Abstract: The use of L-sorbose in synthesis of functionalized cyclopentene derivatives was accomplished. These cyclopentene derivatives are related to those found in naturally occurring jatrophone frameworks and in other bioactive compounds. The formation of allyl α -L-sorbopyranoside was a key synthetic step. Regioselective introduction of protecting groups was followed by the hydrolysis of the allyl glycoside to furnish a fully protected acyclic L-sorbose derivative. This acyclic intermediate was subsequently used to give an orthogonally protected polyhydroxylated cyclopentene, which has potential in further bioactive compound synthesis. The protected cyclopentene itself showed a clear cytotoxic activity when tested against a panel of human cancer cell lines (HT29, LS174T, SW620, A549, HeLa cells).

The occurrence of resistance to anticancer agents is a major obstacle for successful cancer chemotherapy. The emergence of resistance to anticancer drugs, in particular multidrug resistance (MDR) has made many of the available anticancer drugs ineffective.^[1] A glycoprotein, ABCB1, also known as P-glycoprotein, is a membrane protein member of the ABC transporters superfamily. These membrane-embedded transport proteins decrease the intracellular drug accumulation, by and ATP-dependent efflux. This reduces the cytotoxicity of the anticancer agent and enables the tumor cells to survive. Jatrophanes, such as **1-3**, are natural compounds extracted from plants of the genus of *Euphorbia*. A broad range of biological properties have been reported for constituents of the plant extract.^[2] In particular, jatrophanes are potent and specific P-glycoprotein modulators.^[3] In addition, a variety of other biological activities have been reported: inhibitory activity on the mammalian mitochondrial respiratory chain,^[4] antiviral activity,^[5] microtubule interaction,^[6] antiplasmodial activity,^[7] cytotoxicity against various human cancer cell lines^[8].

It has been reported that modifications of the cyclopentene (ring A) of the jatrophone

- [a] Dr. D. Lo Re, Prof. P.V. Murphy, Dr. L. Jones
School of Chemistry
National University of Ireland, Galway
University Road, Galway, Ireland
E-mail: daniele.lore@irbbarcelona.org
E-Mail: paul.v.murphy@nuigalway.ie
- [b] Prof. Ernest Giralt
Institute for Research in Biomedicine (IRB Barcelona), The
Barcelona Institute of Science and Technology
C/Baldiri Reixac 10, Barcelona, E-08028, Spain
- [c] Prof. Ernest Giralt
Department of Organic Chemistry
University of Barcelona
Martí i Franques 1-11, Barcelona, E-08028, Spain

Supporting information for this article is given via a link at the

framework, resulted in increased biological activity (figure 1).^[9] For instance, Hierseman and co-workers^[9] demonstrated that introduction of aromatic lipophilic substituent at C-3 enhanced the ABCB1 inhibitory activity (figure 1). They also show that there is a correlation between overall lipophilicity and ABCB1 inhibition.^[9]

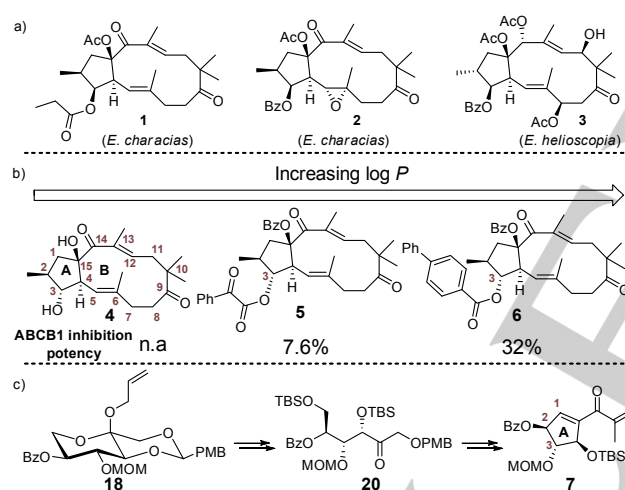
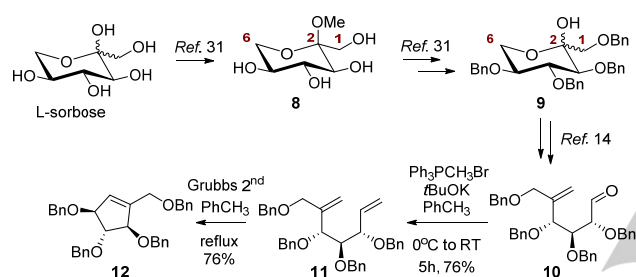


Figure 1. a) Structure of selected jatrophone natural products; b) synthetic jatrophone analogues and their activity against ABCB1; c) orthogonally protected pyranose **18** and open-chain sorbose derivatives **20** and the orthogonal protected cyclopentene **7** prepared herein.

Nevertheless, the potential to prepare cyclopentene derivatives related to those found in **4** and which would ultimately be used to give new jatrophone analogues has formed the motivation for the work described herein. We envisaged that the preparation of orthogonally protected polyhydroxylated cyclopentanol **7**, similar to the ring A of the jatrophone framework, is relevant to the preparation of jatrophone analogues with increased biological activity and for structure-activity relationships. In addition, advanced intermediate **7** can be also used for the

preparation of biologically active cyclopentitols or cyclopentenols. These are polyhydroxylated cyclopentanes,^[10] that display a plethora of biological activity such as found for the glycosidase inhibitors trehazolin and mannostatin,^[10a] [11] the anticancer and antibiotic pactamycin,^[12] and the insecticide ryanodine.^[13] In addition, cyclopentenols, are also important because of their presence in numerous biologically active targets such as the antibiotic pentenomycin,^[14] the anti-inflammatory monotropein,^[15] and the anticancer compound (-)-neplanocin A.^[16]

It was envisaged that the construction of the polyhydroxylated cyclopentene could be achieved through a ring-closing metathesis^[10c, 17] (RCM) reaction of fully protected diene such as that in **11**. Since RCM could be challenging in such a densely substituted diene,^[18] we first prepared **11** in order to validate the synthetic strategy.



Scheme 1. Preliminary validation of the synthetic strategy from L-sorbose: synthesis of per-O-benzylated cyclopentane **12**.

Compound **9** has been prepared from L-sorbose previously.^[19] However, in our hands, attempts to simultaneously install olefin at C6 and C2 through directly oxidation of **9** followed by a concomitant double Wittig reaction were unsuccessful. Oxidation of the latent alcohol of **9** under Swern conditions followed by Wittig reaction only gave a complex mixture while treatment of **9** with the Dess-Martin reagent gave no reaction. For these reasons, aldehyde **10** was first prepared as reported^[19] and then treated with $\text{Ph}_3\text{PCH}_2\text{Br}$ and $t\text{BuOK}$ to give the desired diene **11**. The RCM of **11** using the Grubbs 2nd generation catalyst at room temperature only gave only recovered starting material. However, when the RCM was carried out by heating in refluxing toluene, the polyhydroxylated cyclopentene **12** was isolated in good yield (76%, Scheme 1).

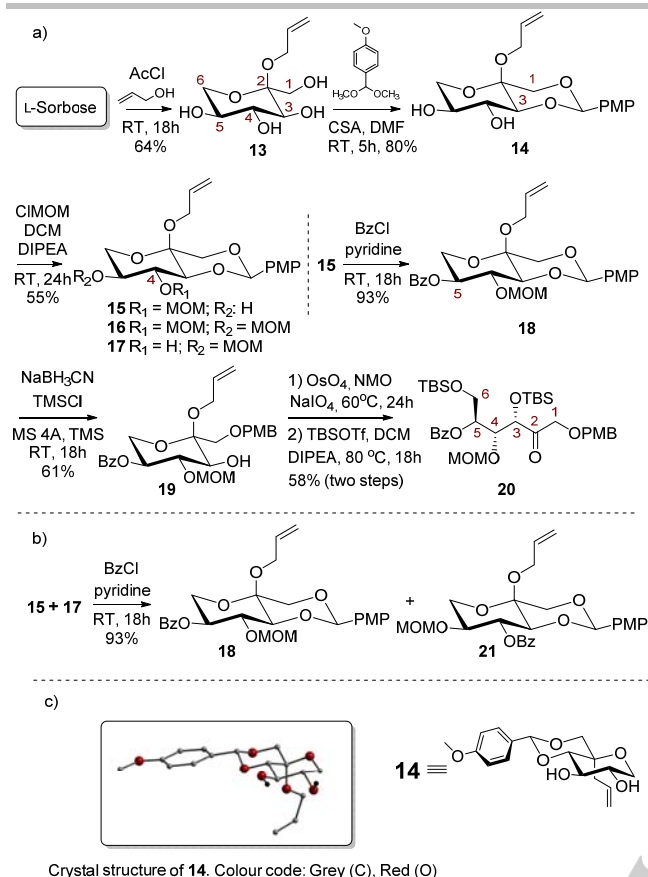
With these encouraging observations in hand, it was next decided to exploit this strategy for the preparation of an orthogonally protected L-sorbose derivative. Chemical manipulation of L-sorbose is often carried out via its methyl L-sorbopyranoside^[19] or its 2,3:4:6-di-O-

isopropylidene- α -L-sorbofuranose.^[18, 20] However, these synthetic approaches suffer drawbacks. In fact, hydrolysis of the dioxolane ring (for the L-sorbofuranose) or hydrolysis of the methyl glycoside (for the L-sorbopyranoside) requires strong acidic conditions, which are not compatible with several functional or protecting groups. On other hand, the allyl group^[21] can be removed in the presence of different protecting groups^[22] under relatively mild conditions.^[23] Since the synthesis of the L-sorbopyranoside **8** is achieved using MeOH in the presence of acetyl chloride (AcCl), we hypothesized that similar conditions could be used for the preparation of the allyl glycoside **13**. In fact, treatment of L-sorbose with allyl alcohol and AcCl gave **13** in 64% yield. However, at this stage we could not establish the stereochemical configuration of **13**. However, ¹H-NMR analysis suggested the formation of the pyranose ring ($J_{3,4} = 9.5$ Hz; $J_{5,6} = 10.4$; $J_{4,5} = 8.7$; $J_{5,6'} = 5.4$) had occurred. Fortunately, regioselective protection of hydroxyl groups at C-1 and C-3 using anisaldehyde dimethyl acetal in presence of camphorsulphonic acid gave **14** in good yield (scheme 2) which crystallized from a mixture of MeOH-AcOEt 3:1. X-Ray crystal structure^[24] determination of the resultant crystals confirmed the formation of the allyl α -L-sorbopyranoside **14** as the main product (see SI). The regioselective protection of diol **14** was next attempted. Unfortunately, the attempted reaction of **14** with TIPSCI in pyridine was not successful. Similar results were obtained when **14** was treated with MOMCl in pyridine. Fortunately, regioselective protection of **14** was achieved using MOMCl and DIPEA in dichloromethane, giving alcohol **15** in moderate yield (55%), together with small amounts of **16** (14%) and a mixture of regioisomers **15** and **17** (16%), after chromatography. We next attempt the protection of the secondary alcohol of **15** as the TBS ether. However, the introduction of the TBS group failed under several conditions (TBSOTf-TEA-THF, TBSOTf-NaH-THF, TBSOTf-DBU, TBSCl-NaH-DMF). Fortunately, treatment of **15** with benzoyl chloride in pyridine gave **18** in excellent yield (93%). The analysis of NMR data for **19** confirmed that the hydroxyl group at C-4 was protected as the MOM ether while the hydroxyl group at C-5 was protected as the benzoate ester. In addition, the mixture of **15** and **17** obtained during regioselective MOM protection of **14** was reacted with BzCl in pyridine giving both **18** and **21** that can be easily separated using chromatography. Treatment of the 3,6-*O*-*p*-methoxybenzylidene acetal **18** with NaCNBH₃ and TMSCl^[25] gave the corresponding 4-*O*-PMB ether **19** in 59% yield.

Next, the protection of the secondary hydroxyl group of **19** was attempted. Unfortunately, protection of **19** as a TIPS ether was unsuccessful after several attempts (using TIPSCI or TIPSOTf, DMAP, DMF, 130 °C or TIPSOTf, NaH, THF, RT), with **19** being recovered unreacted. Surprisingly, even benzylation of **19** failed under several conditions (NaH and BnBr

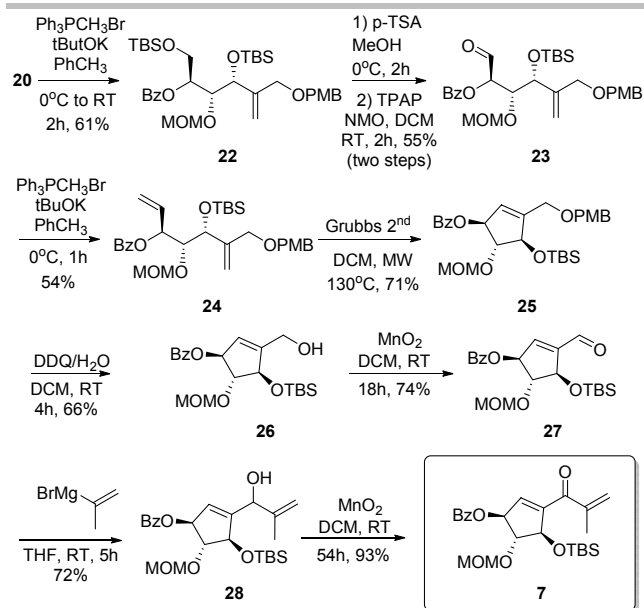
or Dudley's reagent^[26]). Instead, removal of the allyl group, followed by installation of the protecting group at C-3 were studied. However, attempted removal of the allyl protecting group using PdCl₂ at several different conditions gave the desired product in low yields (28-41%). Fortunately, treatment of **19** with OsO₄/NaIO₄^[23b] followed by the simultaneous protection of both the C-3 and C-6 OH groups as TBS ethers gave **20** in good yield (58% over two steps). With **20** in hand, chain branching at C-2 using the Wittig reaction was investigated. Treatment of **20** with Ph₃PCH₃Br and *t*BuOK gave the desired alkene **22** in 61% yield. Regioselective removal of the TBS group at the primary position of **22** using 10 % TsOH in MeOH gave a primary alcohol, which was oxidized using Ley-Griffith conditions and gave aldehyde **23** in good yield. Again, compound **23** was reacted with Ph₃PCH₃Br and *t*BuOK to give diene **24** (Scheme 4). However, the reaction of **24** with the Grubbs 2nd generation catalyst in toluene only gave a complex mixture at different temperatures (from 80 °C to reflux). Fortunately, RCM of **24** in dichloromethane under microwave irradiation gave the orthogonally protected cyclopentene **25** in good yield (71%). Removal of PMB group in **25** was successful using DDQ-H₂O leading to **26** (66%). Treatment of **26** with MnO₂ gave the α,β-unsaturated aldehyde **27** in 74% yield. Aldehyde **27** was then reacted with isopropenylmagnesium bromide to give secondary alcohol **28** (72%) that was finally oxidized with MnO₂ giving the orthogonally protected advanced intermediate **7** in 93% yield (Scheme 3).

Importantly, advanced intermediate **7** has potential to be used for the preparation of analogues of MDR modulators such as jatrophanes and can be also used for the preparation of biologically active cyclopentitols. In addition, intermediate **7** was screened against a panel of human cancer cell lines derived from colon (HT29, Ls174t, SW620), lung (A549) and cervical cancer (HeLa). We took advantage that **7** has a silyl ether, a feature that could increase cellular uptake and enhance anti-proliferative effects. In addition, It has also been demonstrated that no "element-specific" toxicity is associated with organosilicon compounds.^[27] Padron and co-workers have demonstrated that the presence of TBS ether enhance the anti-proliferative effects of tetrahydropyrans derivatives in HL60 (human promyelocytic leukemia) and MCF7 (human breast cancer) cell lines.^[28] Furthermore, trialkylsilyl camptothecin derivatives such as cositecan^[29],^[30] and DB-67^[31] are promising compounds for cancer treatment and are currently in phase III and II clinical trials respectively.



Scheme 2. a) Synthesis of open-chain intermediate **20**; b) resolution of **15-17** mixture; c) crystal structure of **14**.

Compound **7** showed good toxicity in the XTT assay with IC_{50} range of 6.1-35.1 μM . Compound **7** is generally less potent than widely used chemotherapeutics cisplatin or oxaliplatin while in HT29 colon cancer cell line, displayed an activity similar to cisplatin. Previous studies have demonstrated the ability of jathropane diterpenes to reduce the activity of ABC proteins linked with multi-drug resistance (MDR).^[32] Compound **7** can be considered as an analogue of ring A of jathropane (figure 1). In light of that, we decided to test **7** against ABCC2 (MRP2), ABCC3 (MRP3) and ABCB1 (MDR1 or P-gp). At the concentration of 20 μM , compound **7** show weakly inhibit ABCC2 ($10.5 \pm 0.25\%$), ABCC3 ($6.1 \pm 0.35\%$) and ABCB1 ($7.1 \pm 0.65\%$) indicating that truncated^[33] jathropane analogues might have potential to be developed into MDR modulators.



Scheme 3. Synthesis of polyhydroxylated cyclopentene **7**.

In conclusions, we have developed a synthetic approach for the conversion of L-sorbose to allyl α -L-sorbopyranoside (**13**). This intermediate was turned into an orthogonally protected L-sorbopyranose derivative (**18**). The cleavage of the allyl glycoside in **19** is compatible with different protecting group (acidic, basic and single electron oxidation sensitive). Subsequently, we also prepared the orthogonal acyclic L-sorbose derivative (**20**): this intermediate can be used for the preparation of more complex chiral products. We demonstrated its use in preparation of the orthogonally protected polyhydroxylated cyclopentene **7** which could have potential as an intermediate for the preparation of jatrophone analogues or for the preparation of cyclopentitols which are of particular significance because of their presence in a variety of medicinally relevant natural products. Compound, **7** was tested in a panel of human cancer cell lines (HT29, Ls174t, SW620, HeLa, A549) and displayed good cytotoxic activity. In addition, **7** weakly inhibit ABCB1 ABCC2 and ABCC3 demonstrating that it could be used as a starting point for the development of truncated jatrophone analogues as multi drug resistance (MDR) modulators.

	IC ₅₀ (μ M)				
	HT29	Ls174t	SW620	HeLa	A549
Compound 7	35.1	11.2	11.9	6.1	11.2
Cisplatin	45.7	-	-	3.8	2.8
Oxaliplatin	-	1.0 ^a	5.5	-	-

Figure 2. Antiproliferative activity of **7**: IC₅₀ was determined by XTT assay. a: see ref ^[34]

Experimental Section

General methods and materials. All NMR spectra were recorded using a 500 MHz spectrometer at 30 °C. Chemical shifts are reported relative to internal Me₄Si in CDCl₃ (δ 0.0 ppm) for ¹H and CDCl₃ (δ 77.16) for ¹³C at 30 °C, unless otherwise stated. The ¹³C signals were assigned with the aid of HSQC. The ¹H-NMR signals were assigned with the aid of COSY. Coupling constants are reported in Hertz. High resolution mass spectra were measured using an LC Time-of-flight mass spectrometer and were measured in positive and/or negative mode as indicated. TLC were performed on aluminium sheets precoated with Silica Gel 60 (HF254, E. Merck) and spots visualized charring with vanillin solutions. Flash column chromatography was carried out using silica gel 60 (0.040-0.630 mm, E. Merck). Dichloromethane, tetrahydrofuran, MeOH, and toluene were used as obtained from a PureSolv™ solvent purification system. Petroleum ether is the fraction with bp 40-60 °C.

Allyl 1,3-O-(4-methoxybenzylidene)-α-L-sorbopyranoside (14). To a stirred solution of **13** (2.364 g; 10.7 mmol) in DMF (23 mL), camphorsulphonic acid (248 mg; 1.07 mmol) and anisaldehyde dimethyl acetal (1.82 mL; 10.7 mmol) were added. The solution was stirred at room temperature for 5 h. The mixture was diluted with Et₂O (30 mL) and washed several times with water. The solvent was evaporated and flash chromatography (EtOAc-petroleum ether 3:1) gave **14** as a white solid (2.91 g; 80%); m.p. = 104 °C-109 °C; [α]_D - 41 (c 0.69, CHCl₃); ¹H NMR (CDCl₃, 500 MHz): δ 7.48 – 7.36 (d, *J* = 8.8 Hz, 2H, ArCH), 6.91 – 6.82 (d, *J* = 8.7 Hz, 2H, ArCH), 5.99 (ddt, *J*_{trans} = 16.9, *J*_{cis} = 10.5, 5.3 Hz, 1H, OCH₂CH=CH₂), 5.51 (s, 1H, OCHO), 5.37 (dd, 1H, *J* = 17.3, *J*_{gem} = 1.7 Hz, OCH₂CH=CH₂), 5.18 (dd, 1H, *J*_{cis} = 10.6, OCH₂CH=CH₂), 4.26 (dd, 1H, *J* = 12.1, 2.0 Hz, CH₂), 4.18 – 4.11 (m, 1H, OCH₂CH=CH₂), 4.11 – 3.98 (m, 2H, OCH₂CH=CH₂, CH), 3.79 (s, 3H, *J* = 1.4 Hz, OCH₃), 3.75 – 3.62 (m, 2H, CH₂, CH), 3.58 – 3.49 (m, 2H, CH₂), 3.44 (dd, 1H, *J* = 9.8, 2.7 Hz, CH); ¹³C NMR (CDCl₃, 125 MHz): 160.4 (ArC), 134.4 (OCH₂CH=CH₂), 129.7 (ArC), 128.0, (ArCH), 116.7 (OCH₂CH=CH₂), 113.8 (ArCH), 102.7 (OCHO), 92.8 (C-2), 82.0 (CH), 71.2 (CH), 70.7 (CH), 68.2 (CH₂), 63.3 (CH₂), 62.0 (CH₂), 55.5 (OCH₃); HRMS-ESI: calcd for C₁₇H₂₂O₇Na: 361.1263; Found: 361.1266 (M+Na⁺).

Allyl 5-O-benzoyl-1,3-O-(4-methoxybenzylidene)-4-O-(methoxymethoxy)-α-L-sorbopyranoside (18). To a stirred solution of **15** (430 mg; 1.12 mmol) in pyridine (10 mL) at 0 °C, BzCl (195 μL; 1.68 mmol) was added. The mixture was stirred at room temperature for 18 h. TLC (petroleum ether-EtOAc, 2:1) showed a new spot with higher R_f and the absence of

15. The solution was diluted with dichloromethane (20 mL), and washed with 1% HCl (20 mL), dried over Na₂SO₄, filtered and the solvent was removed. Flash chromatography (cyclohexane-EtOAc, 5:1) gave **18** as a yellow oil (508 mg; 93 %); [α]_D: -17.16 (c 0.85, CHCl₃); ¹H NMR (CDCl₃, 500 MHz): 8.09 (m, 2H, ArCH), 7.60–7.55 (m, 1H, ArCH), 7.47–7.43 (m, 4H, ArCH), 6.89 (d, 2H, *J* = 8.8 Hz, ArCH), 6.03 (ddt, 1H, *J*_{trans} = 17.3, *J*_{cis} = 10.6, 5.4 Hz, OCH₂CH=CH₂), 5.59 (s, 1H, OCHO), 5.40 (dd, 1H, *J*_{trans} = 17.2, *J* = 1.7 Hz, OCH₂CH=CH₂), 5.27–5.16 (m, 2H, OCH₂CH=CH₂, H-5), 4.84 (d, 1H, *J* = 6.8 Hz, OCH₂O), 4.67 (d, 1H, OCH₂O), 4.47 (dd, 1H, *J*_{3,4} = *J*_{4,5} = 9.4 Hz, H-4), 4.32 (d, 1H, *J*_{1,1'} = 12.1 Hz, H-1), 4.21 (ddt, 1H, *J* = 12.7, 5.1, 1.6 Hz, OCH₂CH=CH₂), 4.08 (ddt, 1H, *J* = 12.7, 5.1, 1.6 Hz, OCH₂CH=CH₂), 4.01 (dd, 1H, *J*_{6,6'} = 10.6, *J*_{6,5} = 6.4 Hz, H-6), 3.81 (s, 3H, ArOCH₃), 3.74 (d, 1H, H-3), 3.68 – 3.61 (m, 2H, H-1',6'), 3.18 (s, 3H, OCH₂OCH₃); ¹³C NMR (CDCl₃, 125 MHz): δ 165.8 (CO), 160.3 (ArC), 134.4(OCH₂CH=CH₂), 133.5 (ArCH), 129.9 (ArC), 129.9 (ArCH), 129.6 (ArC), 128.6 (ArCH), 127.8 (ArCH), 116.8 (OCH₂CH=CH₂), 113.7 (ArCH), 102.4 (OCHO), 97.3 (OCH₂O), 93.0 (C-2), 82.1 (C-3), 73.0 (C-4), 71.7 (C-5), 68.1 (C-1), 62.3 (OCH₂CH=CH₂), 60.9 (C-6), 55.8 (OCH₂OCH₃), 55.4 (ArOCH₃); HRMS-ESI: calcd for C₂₆H₃₀O₉Na: 509.1788; Found: 509.1788 (M+Na⁺).

5-O-benzoyl-3,6-di-O-(Tert-butyldimethylsilyl)-1-O-(4-methoxybenzyl)-4-O-

(methoxymethoxy)-L-sorbose (20). To a stirred solution of **19** (657 mg; 1.34 mmol) in dioxane (6.5 mL) and H₂O (0.7 mL), NMO (473 mg; 4.039 mmol), OsO₄ (1.419 mL; ~ 0.134 mmol, 2.5% in *t*-BuOH), NaIO₄ (1.146 g; 5.36 mmol) and H₂O (2.6 mL) were added. The resulting solution was stirred at 60 °C for 24 h. TLC (petroleum ether-EtOAc 1:1) showed a new spot with lower R_f and the absence of 19. The mixture was diluted with dichloromethane and washed with H₂O. The organic layers were washed with aq satd Na₂S₂O₃. The organic phase was dried and the solvent was removed. The crude mixture was dissolved in DMF (6.5 mL), DIPEA (1.87 mL; 10.72 mmol) and TBSOTf (1.229 mL; 5.36 mmol) were added and the resulting solution was stirred at 80 °C for 18h. TLC (petroleum ether-EtOAc 1:1) showed a new spot with higher R_f and the absence of starting material. The solution was diluted with dichloromethane and washed with H₂O. The organic phase was dried and the solvent was removed. Flash chromatography (cyclohexane-EtOAc, 30:1 to 10:1 gradient elution) gave **20** as a yellow oil (525 mg; 58 % over two steps); [α]_D: -19.6° (c 0.41, CHCl₃); ¹H NMR (CDCl₃, 500 MHz): δ 8.03–7.97 (m, 2H, ArCH), 7.55–7.50 (m, 1H, ArCH), 7.41 (t, 2H, *J* = 7.8 Hz, ArCH), 7.09 (d, 2H, *J* = 8.6 Hz, ArCH), 6.79 (d, 2H, *J* = 8.6 Hz, ArCH), 5.39 (td, 1H, *J* = 5.8, 4.3 Hz, H-5), 4.75 (d, 2H, *J* = 1.6 Hz, CH₂), 4.50 (d, 1H, *J* = 5.1 Hz, H-3), 4.34 – 4.24 (m, 2H, CH₂),

4.22 – 4.13 (m, 3H, H-4 and CH_2), 3.85 (dd, 2H, $J = 5.9, 1.4$ Hz, H-6), 3.78 (s, 3H, $ArOCH_3$), 3.39 (s, 3H, OCH_2OCH_3), 0.90 (s, 9H, $C(CH_3)_3$), 0.86 (s, 9H, $C(CH_3)_3$), 0.08 (s, 3H, $SiCH_3$), 0.03 (m, 9H, $3SiCH_3$); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 206.3 (C=O), 165.8 (C=O), 159.4 (ArC), 133.2 (ArCH), 130.0 (ArCH), 129.9 (ArC), 129.6 (ArCH), 129.5 (ArC), 128.5 (ArCH), 113.8 (ArCH), 98.2 (CH_2), 77.5 (C-4), 76.3 (C-3), 73.1 (CH_2), 72.9 (CH_2), 60.5 (C-5), 56.4 (CH_2), 55.4 ($ArOCH_3$), 25.9 ($C(CH_3)_3$), 18.2 ($C(CH_3)_3$), -4.8 ($SiCH_3$), -4.8 ($SiCH_3$), -5.2 ($SiCH_3$), -5.4 ($SiCH_3$); HRMS-ESI: calcd for $C_{35}H_{56}O_9Si_2Na$: 699.3361; Found: 699.3354 ($M+Na^+$).

(1S,4R,5R)-4-(Tert-butyl dimethylsilyloxy)-3-methacryloyl-5-

(methoxymethoxy)cyclopent-2-en-1-yl benzoate (7). To a stirred solution of **28** (20.0 mg; 0.045 mmol) in dichloromethane (1.0 mL), MnO_2 (39 mg; 0.45 mmol) was added. The resulting solution was stirred at room temperature for 48 h. The mixture was filtered through celite with dichloromethane (50 mL) and the solvent was removed. The crude was re-dissolved in dichloromethane (1.0 mL), MnO_2 (20 mg; 0.23 mmol) was added and the resulting mixture was stirred at room temperature for additional 6 h. The mixture was filtered through celite with dichloromethane (50 mL) and the solvent was removed. Flash chromatography (EtOAc-cyclohexane 1:10) gave **7** as a yellow oil (18.7 mg; 93%); 1H NMR ($CDCl_3$, 500 MHz): δ 8.12 – 8.06 (m, 2H, ArCH), 7.61 – 7.56 (m, 1H, ArCH), 7.46 (t, 2H, $J = 7.8$ Hz, ArCH), 6.16 (d, 1H, $J_{1,2} = 1.9$ Hz, H-2), 6.00 (s, 1H, $C(Me)=CH_2$), 5.90 (s, 1H, $C(Me)=CH_2$), 5.71 (dd, 1H, $J_{1,5} = 4.4$ Hz, H-1), 5.02 (d, 1H, $J_{4,5} = 4.0$ Hz, H-4), 4.77 (q, 2H, $J = 6.8$ Hz, OCH_2O), 4.29 (appt, 1H, $J_{1,4} = J_{1,5} = 4.2$ Hz, H-5), 3.33 (s, 3H, OCH_3), 1.93 (s, 3H, $C(Me)=CH_2$), 0.85 (s, 9H, $C(CH_3)_3$), 0.15 (s, 3H, $SiCH_3$), 0.07 (s, 3H, $SiCH_3$); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 194.5 (C=O), 166.1 (C=O), 146.4 (C), 144.5 (C), 133.4 (ArCH), 133.2 (C-2), 130.0 (C), 129.9 (ArCH), 128.8 ($C(Me)=CH_2$), 128.6 (ArCH), 97.2 (OCH_2O), 90.6 (C-5), 79.9 (C-1), 78.7 (C-4), 56.1 (OCH_3), 25.8 ($C(CH_3)_3$), 18.1 ($C(Me)=CH_2$), 17.4 ($C(CH_3)_3$), -4.6 ($SiCH_3$), -5.0 ($SiCH_3$); HRMS-ESI: calcd for $C_{24}H_{34}O_6SiNa$: 469.2022; Found: 469.2015.

Cell Culture. A549 (non-small cell lung cancer, human), HT29 (colorectal adenocarcinoma, human), SW620 (colorectal, Dukes' type C, human) and Ls174t (colorectal, Dukes' type B, human), HeLa (cervix adenocarcinoma, human) cells were grown in 75 cm^2 culture flasks (Corning® Flask) as adherent monolayer cultures in Dulbecco's Modified Eagle Medium (DMEM) (GIBCO, ref. 41966-029). Culture mediums were supplemented with 10% heat-inactivated fetal bovine serum, and with Penicillin/Streptomycin (Gibco, 15140-122). Cultures were maintained at 37 °C in a humidified atmosphere containing 5% CO_2 and 95% air.

Inhibition of Cell Viability Assay. Drug effects on exponentially growing tumour cells were determined using XTT assay as described previously.³⁵ A549, HT29, SW620, Ls174t, HeLa cells were seeded at a density of 3000 cells/well in 96-well plates and incubated for 24h. Thereafter, cancer cells were exposed to drugs at different concentrations during 72h. At 72h, 50 μ L of XTT/ECR 1:50 solution was added and incubated for a further 4 h at 37 °C. Absorbance measured at 475 nm was converted to percentages. UV-vis absorbance was measured at 475 nm using a microplate reader. Experiments were performed in triplicate for each drug concentration and carried out independently at least three times. The interpolation analysis was done using dose-dependent inhibition pattern (\log^{3d} vs. normalized response {Variable slope}) with Prism version 5.00 software (GraphPad Software, USA).

Drug transporter inhibition assay. Cells are seeded in a 96-well culture plate typically at 20,000 cells/well and are used on days 2 or 3 post-seeding. On the day of assay the test compound is prepared in assay buffer (HBSS-HEPES, pH 7.4), added to the cell plate, and pre-incubated at 37 °C for 15 min. Subsequently substrate is added to the plate followed by 20-min incubation at 37 °C. The plate is then washed with cold assay buffer followed by fluorescence reading for assays with fluorogenic substrates. Cell lines: MDR1-MDCKII (Transporter: P-gp, substrate: Calcein AM, positive control Verapamil IC_{50} = 29 μ M); MRP2-HEK (Transporter: MRP2, substrate CDCF, positive control MK571 IC_{50} = 14 μ M); -HEK; MRP3-HEK (Transporter: MRP2, substrate CDCF, positive control MK571 IC_{50} = 12 μ M).

Acknowledgements ((optional))

This work was supported by Science Foundation Ireland (grant Nos. 07/IN.1/B966 and 11/TIDA/B2047). The research leading to these results also received funding from the People Programme (Marie Curie Actions) of the European Union's Seventh Framework Programme (FP7/2007-2013) under grant agreement number PIEF-GA-2011-299042 and from the European Union's Seventh Framework Programme for research, technological development and demonstration under grant agreement no 600404 and from MINECO-FEDER (Bio2013-40716-R). IRB Barcelona is the recipient of a Severo Ochoa Award of Excellence from MINECO (Government of Spain).

Keywords: glycomimetics • chiral pool • carbohydrate • orthogonal protection

[1] E. Borowski, M. M. Bontemps-Gracz, A. Piwkowska, *Acta Biochim Pol* **2005**, 52, 609-627.

- [2] H. Lage, N. Duarte, C. Coburger, A. Hilgeroth, M. J. Ferreira, *Phytomedicine* **2010**, *17*, 441-448.
- [3] aG. Corea, E. Fattorusso, V. Lanzotti, O. Tagliatalata-Scafati, G. Appendino, M. Ballero, P.-N. Simon, C. Dumontet, A. Di Pietro, *Journal of Medicinal Chemistry* **2003**, *46*, 3395-3402; bG. Corea, E. Fattorusso, V. Lanzotti, R. Motti, P. N. Simon, C. Dumontet, A. Di Pietro, *Planta Med* **2004**, *70*, 657-665; cG. Corea, E. Fattorusso, V. Lanzotti, R. Motti, P. N. Simon, C. Dumontet, A. Di Pietro, *J Med Chem* **2004**, *47*, 988-992; dE. Barile, M. Borriello, A. Di Pietro, A. Doreau, C. Fattorusso, E. Fattorusso, V. Lanzotti, *Organic & Biomolecular Chemistry* **2008**, *6*, 1756-1762.
- [4] L. Betancur-Galvis, J. Checa, J. A. Marco, E. Estornell, *Jatrophane diterpenes from the latex of Euphorbia obtusifolia with inhibitory activity on the mammalian mitochondrial respiratory chain*, *Planta Med.* 2003 Feb;69(2):177-8.
- [5] I. Mucsi, J. Molnar, J. Hohmann, D. Redei, *Cytotoxicities and anti-herpes simplex virus activities of diterpenes isolated from Euphorbia species*, *Planta Med.* 2001 Oct;67(7):672-4.
- [6] R. M. Buey, I. Barasoain, E. Jackson, A. Meyer, P. Giannakakou, I. Paterson, S. Mooberry, J. M. Andreu, J. F. Diaz, *Chem Biol* **2005**, *12*, 1269-1279.
- [7] A. M. Adelekan, E. A. Prozesky, A. A. Hussein, L. D. Urena, P. H. van Rooyen, D. C. Liles, J. J. Meyer, B. Rodriguez, *J Nat Prod* **2008**, *71*, 1919-1922.
- [8] C. Valente, M. Pedro, J. R. Ascenso, P. M. Abreu, M. S. Nascimento, M. J. Ferreira, *Planta Med* **2004**, *70*, 244-249.
- [9] C. Schnabel, K. Sterz, H. Müller, J. Rehbein, M. Wiese, M. Hiersemann, *The Journal of Organic Chemistry* **2011**, *76*, 512-522.
- [10] aA. Bercibar, C. Grandjean, A. Siriwardena, *Chem Rev* **1999**, *99*, 779-844; bP. M. Flatt, T. Mahmud, *Nat Prod Rep* **2007**, *24*, 358-392; cV. B. Kurteva, C. A. Afonso, *Chem Rev* **2009**, *109*, 6809-6857.
- [11] aB. E. Ledford, E. M. Carreira, *Journal of the American Chemical Society* **1995**, *117*, 11811-11812; bG. Wegener, V. Tschiedel, P. Schloder, O. Ando, *J Exp Biol* **2003**, *206*, 1233-1240.
- [12] G. Guha, W. Lu, S. Li, X. Liang, M. F. Kulesz-Martin, T. Mahmud, A. K. Indra, G. Ganguli-Indra, *PLoS one* **2015**, *10*, e0125322.
- [13] A. K. Isaacs, S. Qi, R. Sarpong, J. E. Casida, *Chemical Research in Toxicology* **2012**, *25*, 1571-1573.
- [14] aK. Umino, T. Furumai, N. Matsuzawa, Y. Awataguchi, Y. Ito, *J Antibiot* **1973**, *26*, 506-512; bK. Umino, N. Takeda, Y. Ito, T. Okuda, *Chem Pharm Bull* **1974**, *22*, 1233-1238.

- [15] J. Choi, K. T. Lee, M. Y. Choi, J. H. Nam, H. J. Jung, S. K. Park, H. J. Park, *Biol Pharm Bull* **2005**, *28*, 1915-1918.
- [16] G. Chandra, Y. W. Moon, Y. Lee, J. Y. Jang, J. Song, A. Nayak, K. Oh, V. A. Mulamoottil, P. K. Sahu, G. Kim, T.-S. Chang, M. Noh, S. K. Lee, S. Choi, L. S. Jeong, *Journal of Medicinal Chemistry* **2015**, *58*, 5108-5120.
- [17] aM. Comin, amp, x, J. a, J. B. Rodriguez, *Tetrahedron* **2000**, *56*, 4639-4649; bF. Thorstensson, I. Kvarnström, D. Musil, I. Nilsson, B. Samuelsson, *Journal of Medicinal Chemistry* **2003**, *46*, 1165-1179; cZ. J. Xue, P. Chen, S. Y. Peng, Y. C. Li, *Tetrahedron* **2006**, *62*, 199-204; dP. Radha Krishna, R. R. Kadiyala, *Tetrahedron Letters* **2012**, *53*, 744-747; eJ. D. Padwal, D. V. Filippov, B. D. Narhe, S. Aertssen, R. J. Beuving, J. C. Benningshof, G. A. van der Marel, H. S. Overkleeft, M. van der Stelt, *Bioorg Med Chem* **2015**, *23*, 2650-2655.
- [18] D. Lo Re, F. Franco, F. Sánchez-Cantalejo, J. A. Tamayo, *European Journal of Organic Chemistry* **2009**, *2009*, 1984-1993.
- [19] I. Cumpstey, S. Gehrke, S. Erfan, R. Cribru, *Carbohydr Res* **2008**, *343*, 1675-1692.
- [20] aI. Izquierdo, J. A. Tamayo, M. Rodríguez, F. Franco, D. Lo Re, *Tetrahedron* **2008**, *64*, 7910-7913; bJ. A. Tamayo, F. Franco, D. Lo Re, *Synlett* **2010**, *2010*, 1323-1326; cC. O. Brien, P. V. Murphy, *Journal of Carbohydrate Chemistry* **2011**, *30*, 626-640; dC. O'Reilly, C. O'Brien, P. V. Murphy, *Tetrahedron Letters* **2009**, *50*, 4427-4429; eS. Barron, P. V. Murphy, *MedChemComm* **2014**, *5*, 1150-1158.
- [21] H. Kunz, H. Waldmann, in *Comprehensive Organic Synthesis*, Pergamon, Oxford, **1991**, pp. 631-701.
- [22] T. J. Boltje, C. Li, G. J. Boons, *Org Lett* **2010**, *12*, 4636-4639.
- [23] aS. Chandrasekhar, C. Raji Reddy, R. Jagadeeshwar Rao, *Tetrahedron* **2001**, *57*, 3435-3438; bP. I. Kitov, D. R. Bundle, *Organic Letters* **2001**, *3*, 2835-2838; cH. Tsukamoto, T. Suzuki, Y. Kondo, *Synlett* **2007**, *2007*, 3131-3136.
- [24] aP. McArdle, P. Daly, D. Cunningham, *Journal of Applied Crystallography* **2002**, *35*, 378; bG. Sheldrick, *Acta Crystallographica Section A* **1990**, *46*, 467-473.
- [25] T. Nagano, J. Pospisil, G. Chollet, S. Schulthoff, V. Hickmann, E. Moulin, J. Herrmann, R. Muller, A. Furstner, *Chemistry* **2009**, *15*, 9697-9706.
- [26] aK. W. C. Poon, S. E. House, G. B. Dudley, *Synlett* **2005**, *2005*, 3142-3144; bJ. Tummatorn, P. A. Albinia, G. B. Dudley, *The Journal of Organic Chemistry* **2007**, *72*, 8962-8964.
- [27] A. K. Franz, S. O. Wilson, *Journal of Medicinal Chemistry* **2013**, *56*, 388-405.

[28]aO. J. Donadel, T. Martin, V. S. Martin, J. Villar, J. M. Padron, *Bioorg Med Chem Lett* **2005**, *15*, 3536-3539; bR. Carrillo, L. G. Leon, T. Martin, V. S. Martin, J. M. Padron, *Bioorg Med Chem Lett* **2006**, *16*, 6135-6138; cR. Carrillo, L. G. Leon, T. Martin, V. S. Martin, J. M. Padron, *Bioorg Med Chem Lett* **2007**, *17*, 780-783.

[29]A. Daud, N. Valkov, B. Centeno, J. Derderian, P. Sullivan, P. Munster, P. Urbas, R. C. Deconti, E. Berghorn, Z. Liu, F. Hausheer, D. Sullivan, *Clin Cancer Res* **2005**, *11*, 3009-3016.

[30]V. J. Venditto, E. E. Simanek, *Mol Pharm* **2010**, *7*, 307-349.

[31]E. Tsakalozou, E. D. Adane, Y. Liang, S. M. Arnold, M. Leggas, *Cancer Chemother Pharmacol* **2014**, *74*, 45-54.

[32]aN. A. Colabufo, F. Berardi, M. Cantore, M. Contino, C. Inglese, M. Niso, R. Perrone, *Journal of Medicinal Chemistry* **2010**, *53*, 1883-1897; bP. D. W. Eckford, F. J. Sharom, *Chemical Reviews* **2009**, *109*, 2989-3011.

[33]aJ.-Y. Wach, K. Gademann, *Synlett* **2012**, *2012*, 163-170; bK. Majchrzak, D. Lo Re, M. g. Gajewska, M. g. Bulkowska, A. Homa, K. Paw?owski, T. Motyl, P. V. Murphy, M. Król, *PLoS one* **2013**, *8*, e76789; cD. Lo Re, Y. Zhou, M. Nobis, K. I. Anderson, P. V. Murphy, *ChemBioChem* **2014**, *15*, 1459-1464; dD. Lo Re, Y. Zhou, J. Mucha, L. F. Jones, L. Leahy, C. Santocanale, M. Krol, P. V. Murphy, *Chemistry – A European Journal* **2015**, *21*, 18109-18121; eC. Gaul, J. T. Njardarson, D. Shan, D. C. Dorn, K. D. Wu, W. P. Tong, X. Y. Huang, M. A. Moore, S. J. Danishefsky, *J Am Chem Soc* **2004**, *126*, 11326-11337; fD. Shan, L. Chen, J. T. Njardarson, C. Gaul, X. Ma, S. J. Danishefsky, X.-Y. Huang, *Proceedings of the National Academy of Sciences of the United States of America* **2005**, *102*, 3772-3776.

[34]R. Yin, S. Gou, Y. Sun, X. Liu, *Bioorg Med Chem* **2012**, *20*, 1461-1467.