Synthesis of 2,8-disubstituted-4,7-dioxatricyclo[3.2.1.0^{3,6}]octane and 2,6-dioxabicyclo[3.2.0]heptane derivatives starting from furan

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Dedicated to Prof. Julio Alvárez-Builla. University of Alcalá de Henares

Abstract
The title compounds have been prepared from previously synthesized 2-*endo*-acetoxy-3-*endo*-hydroxy-7-oxabicyclo[2.2.1]hept-5-ene and 3-acetoxy-4-hydroxy-2,5-divinyl-furan *via* intramolecular electrophilic cyclization. Both types of compounds constitute new functionalized oxetane ring systems.

Keywords: Oxetanes, electrophilic addition, dioxatricyclooctane, dioxabicyclooctane

Introduction

The oxetane ring system[1] constitutes subunits of important naturally occurring compounds such as taxoids,[2] thromboxane A_2 (TXA_2),[3] some sesquiterpene lactones,[4] diterpenoids[5] and medium-sized cyclic ethers.[6] On the other hand these compounds are valuable monomers in different polymerization processes[7] being also well established synthetic intermediates[8] and useful tools in drug discovery.[9]

On the other hand, compounds possessing the 4,7-dioxatricyclo[3.2.1.0^{3,6}]octane and 2,6-dioxabicyclo[3.2.0]heptane skeletons (structures **1** and **2** respectively, Figure 1) constitute two interesting class of compounds bearing an oxetane subunit. Compounds with structure **1** are efficient herbicides and plant-growth regulators and at least four patents concerning the synthesis and applications of products showing this motif have been reported.[10] On the other hand, the bicyclic oxetane **2** constitutes a "sugar" subunit of several conformationally restricted nucleosides. These compounds have been extensively investigated as building blocks for oligonucleotides with important therapeutic and diagnostic applications.[11] The "oxetane T" **3** (Figure 1) is an example of this type of molecules.[12]

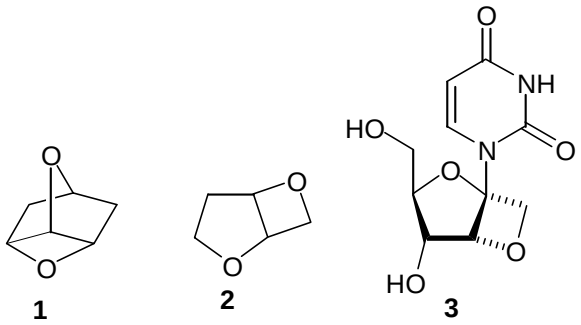
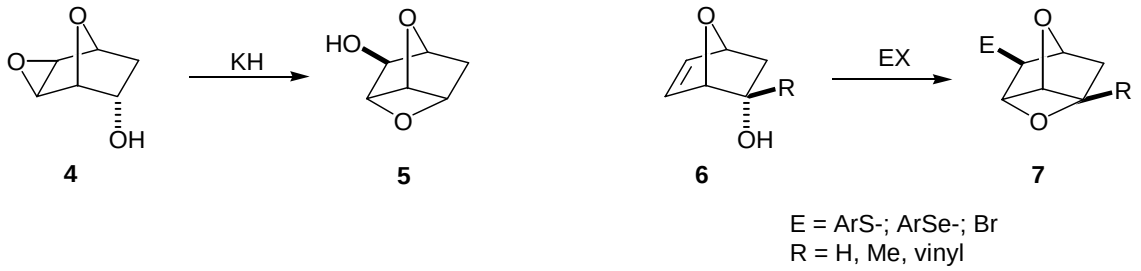


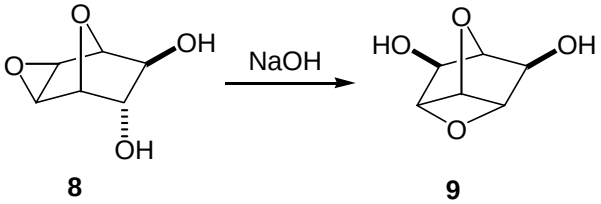
Figure 1. The 4,7-dioxatricyclo[3.2.1.0^{3,6}]octane and 2,6-dioxabicyclo[3.2.0]heptane skeletons.

The synthesis of 8-hydroxy derivatives of **1** (compound **5**, Scheme 1) has been reported using intramolecular ring-opening of 5,6-*exo*-epoxy-7-oxa-2-*endo*-hydroxynorbornane **4**.[13,14] Moreover several accounts concerning the preparation of other 8-substituted derivatives of **1** have been carried out by intramolecular halo-, arylsulfanyl- and arylselenil etherification[15] of 2-*endo*-hydroxy-7-oxabicyclo[2.2.1]hept-5-ene derivatives **6**.[16] It should be pointed out that compounds with structure **7** have been used as starting materials in some useful synthetic transformations.[17] Regarding compounds **2** (Figure 1), they have usually been synthesized by photochemical cycloaddition reactions of 2,3-dihydrofuran derivatives and carbonyl compounds (the Paternó-Büchi reaction).[18]



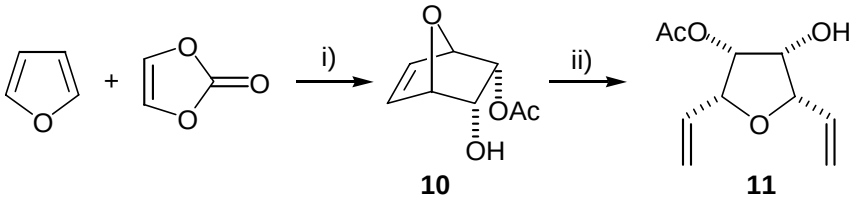
Scheme 1. Synthesis of 4,7-dioxatricyclo[3.2.1.0^{3,6}]octane derivatives.

The 2,8-disubstituted derivatives of **1** have, to the best of our knowledge, never been synthesized with the exception of the dihydroxy compound **9** which was obtained (60 %) by reaction of the dihydroxyepoxide **8** with NaOH followed by crystallization of the polymeric reaction crude (Scheme 2).[19]



Scheme 2. Synthesis of 2,8-dihydroxy-4,7-dioxatricyclo[3.2.1.0^{3,6}]octane **9.**

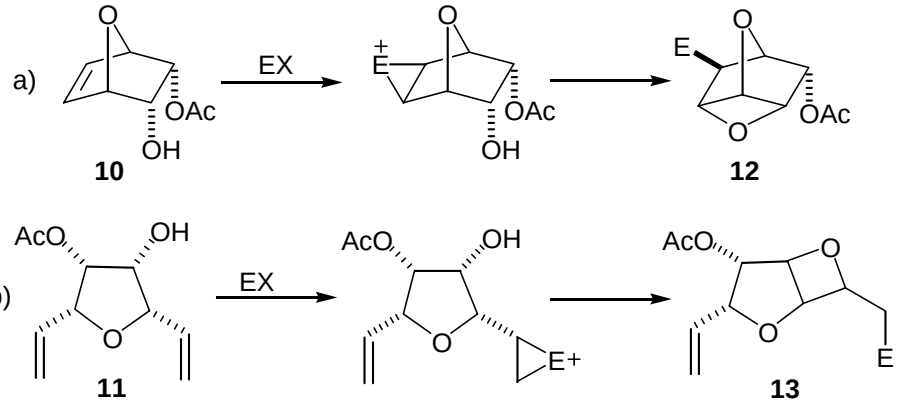
Recently[20] we have reported the synthesis of enantiomerically enriched 7-oxanorbornene derivative **10** (Scheme 3) *via* Diels-Alder cycloaddition between furan and vinylene carbonate followed by hydrolysis and enzymatic desymmetrization. Compound **10** may be transformed into 2,5-divinyl-3-acetoxy-4-hydroxytetrahydrofuran **11** *via* ring-opening metathesis (ROM)-cross metathesis (CM) tandem reactions ("metathesis rearrangement") using ethylene as cross metathesis partner.



i) 1. Diels-Alder reaction; 2. Enzymatic desymmetrization.
ii) ROM-CM tandem reactions.

Scheme 3. General sequence for the synthesis of compounds **10** and **11.**

Compound **10** is a suitable starting material for the synthesis of 2,8-disubstituted-4,7-dioxa-tricyclo[3.2.1.$0^{3,6}$]octane derivatives **12** *via* intramolecular etherification (*endo* hydroxyl group at the position 2 of the starting material **10**) of the *epi*-cation intermediate generated by electrophilic addition on the double bond of **10** (Scheme 4a). Compounds **12** are fully and differentially substituted tricyclic systems, potentially useful as herbicidal agents or as intermediates in other synthetic transformations. On the other hand compound **11** shows an homoallylic alcohol functionality and, in this way, the electrophilic addition to the double bond at position 5 could be an interesting procedure for the synthesis of new functionalized 2,6-dioxabicyclo[3.2.0]heptane derivatives such as **13** (Scheme 4b). In addition this reaction may constitute a possibility for the differentiation of both double bonds at position 2 and 5.



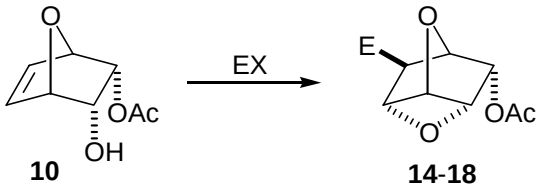
Scheme 4. Intramolecular etherification of compounds **10** and **11.**

Thus, the exploration of this synthetic approach to compounds **12** and **13** constitutes the objective of the present report.

Results and Discussion

Synthesis of 2,8-disubstituted-4,7-dioxatricyclo[3.2.1.0^{3,6}]octane derivatives 12

The reaction of compound **10** with *N*-chlorosuccinimide (NCS), *N*-bromosuccinimide (NBS), *N*-Iodosuccinimide (NIS), *p*-nitrophenylsulfanylchloride and phenylselenylchloride afforded oxetanes **14-18** in moderate-good yields (Scheme 5). The structure of compounds **14-18** was secured by spectroscopic (^{1}H NMR, ^{13}C NMR, IR), combustion analysis and comparison with data previously published for related compounds (see references 14a and 16b-d). The assignments of proton (^{1}H NMR) and carbon (^{13}C NMR) signals have been carried out by DEPT 135, HMQC and HMBC experiments.

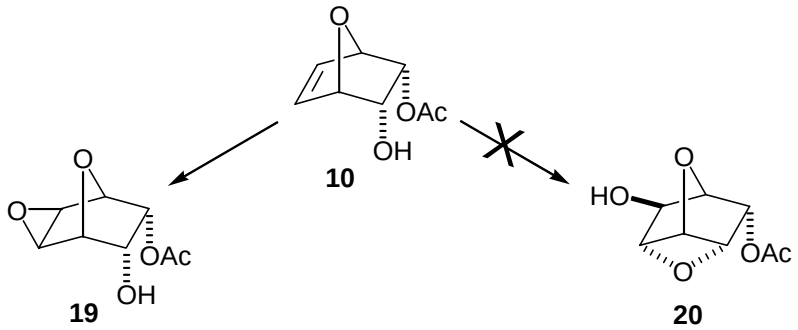


10 **14-18**

14 (X = Cl, 90 %);
15 (X = Br, 89 %);
16 (X = 4-NO_2-C_6H_4-S-, 48 %);
17 (X = C_6H_5-Se-, 55 %);
18 (X = I, 34 %, see text).

Scheme 5. Synthesis of new 2,8-disubstituted-4,7-dioxatricyclo[3.2.1.0^{3,6}]octane derivatives **14-18.**

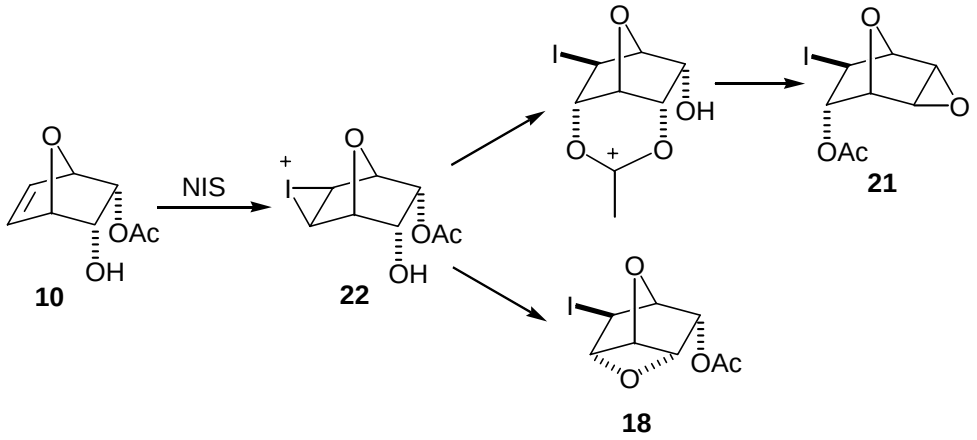
On the other hand, reaction of **10** with m-CPBA afforded oxirane **19** (89 %, Scheme 6). No trace of the related hydroxyderivative **20** was observed in the reaction crude. It should be pointed out that the herbicidal activity of compounds with structure of 3,8-dioxatricyclo[3.2.1.0^{2,4}]octane such as **20** has been reported.[21]



Scheme 6. Reaction of compound **10** with m-CPBA.

The reaction of compound **10** with NIS deserves some comments. In this case a mixture of the iododerivative **18** and iodoepoxide **21** (58 %) was isolated after column chromatography.

Change of the experimental conditions (ratio **10**:NIS and reaction time) did not modify this result. The formation of compounds **18** and **21** appears to be the result of a competition between two intramolecular attacks (hydroxy- or acetoxy- groups) on the epiiodoium cation intermediate **22** (Scheme 7).[22] It should be indicated that this reaction path has previously been proposed, for instance, in the 1,2-hydroxyiodination of acetoxycyclohex-2-ene.[23]

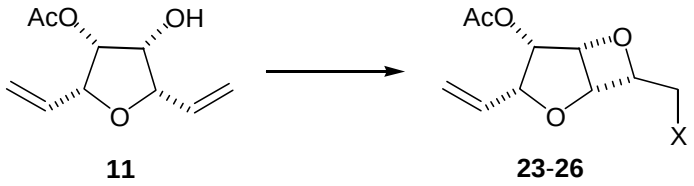


Scheme 7. Reaction of compound **10** with NIS.

This different behaviour of compound **10** in their reaction with NIS may be explained on the basis of the grater stability of cation **22** regarding the analogous derived from NCS and NBS.[24]

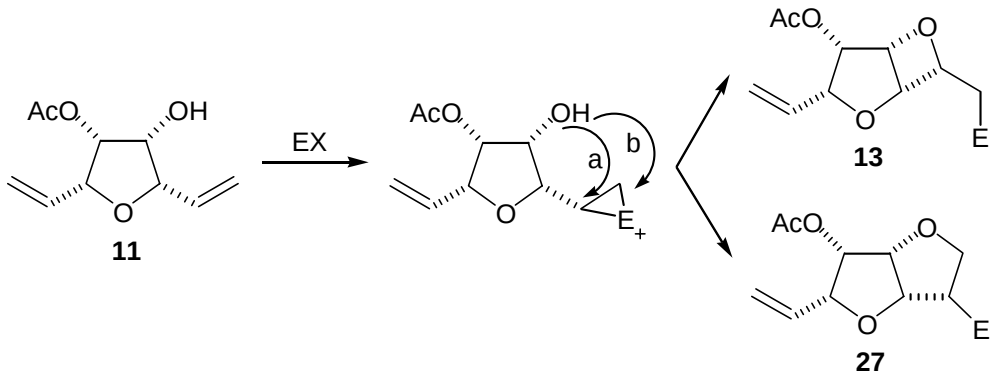
Synthesis of substituted 2,6-dioxabicyclo[3.2.0]heptane derivatives 13

The reaction of compound **11** with NIS, NBS, NIS and *p*-nitrophenylsulphanylchloride afforded the expected oxetanes **23-26** in moderate-good yields. The results are summarized in Scheme 8.



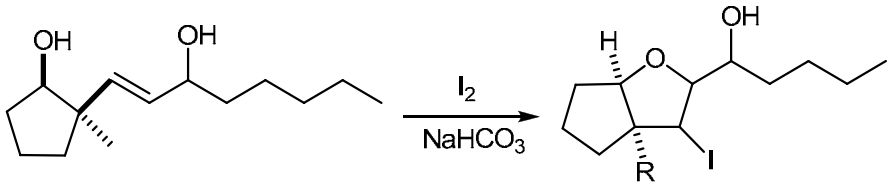
Scheme 8. Synthesis of new 2,6-dioxabicyclo[3.2.0]heptane derivatives.

The synthesis of 2,6-dioxabicyclo[3.2.0]heptane derivatives from 2-vinyl-3-hydroxytetrahydro-furan precursors has never been reported using this methodology. Note that from compound **11** two modes of cyclization are possible: the 4-*exo* mode (a, Scheme 9) giving the oxetane **13** and the 5-*exo* mode (b, Scheme 9) giving the tetrahydrofuran **27**.



Scheme 9. Oxetane vs. tetrahydrofuran formation in the electrophilic cyclization of compound **11.**

In the case of electrophilic cyclization of a homoallylic alcohol incorporated into a cyclic structure such as **11** some precedents indicate that the tetrahydrofuran derivative is the only reaction product. A representative example is shown in Scheme 10.[25] In this way the formation of compounds **23**-**26** is noteworthy.[26]



Scheme 10. Tetrahydrofuran formation in the electrophilic cyclization of a cyclic homoallylic alcohol.

Conclusions

In this report two types of oxetane derivatives have been synthesized using the intramolecular etherification protocol. Firstly we have described an efficient method for the preparation of 2,8-disubstituted-4,7-dioxatricyclo[3.2.1.$0^{3,6}$]octane derivatives starting from readily accessible oxanorbornenic compounds. Different types of substituents have been introduced at position 8 and the final tricyclic systems constitute promising materials on the biological (potentially herbicides by analogy with other previously described) and synthetic point of view. On the other hand, the electrophilic heterocyclization of 2,5-divinyltetrahydrofuran derivatives allows for the preparation of functionalized 2,6-dioxabicyclo[3.2.0]heptane being the oxetane the only product observed. The described reaction also allowed for the chemical differentiation of both double bonds at position 2 and 5 of the starting materials.

Experimental Section

General. All reactions were carried out under an argon atmosphere employing standard techniques. All solvents were reagent grade. Dichloromethane was freshly distilled from calcium hydride. All other reagents and solvents were used as supplied. Flash chromatography was performed with silica gel 60 (230-400 mesh). Yields refer to cromatography and spectroscopically pure compounds. ^{1}H And ^{13}C Nuclear Magnetic Resonance spectra were recorded on a Bruker AM-300 (300 MHz) and a Bruker AVIII-700 (700 MHz) NMR spectrometer in deuterocloroform, deuterated acetone and hexadeuterobenzene. Assignments of proton (^{1}H NMR) and carbon (^{13}C NMR) signals have been secured by DEPT 135, COSY 45, HMQC and HMBC experiments. Coupling constants are given in Hz, and chemical shifts are expressed as δ values in ppm. Melting points are uncorrected and were determined using a Gallenkamp instrument. IR spectra were obtained on a Perkin-Elmer apparatus in solution of $CHCl_3$. Elemental analyses were carried out using a Perkin-Elmer 2400 CHN apparatus at the Complutense University, Madrid.

Starting materials. The synthesis of compounds **10** and **11** have been previously described.[20]

Synthesis of compounds (14-18). General procedure

To a solution of 1.0 eq. of **10** in acetonitrile (50 mL/mmol) at r.t., 1.1 eq. of the electrophilic reagent was added. The solution was stirred at r.t. during 24 h. After this time the solvent was removed at vacuo and the reaction crude was purified by column chromatography (SiO_2, hexane:AcOEt, 7:3).

Compound (14). From 27 mg of **10** (0.16 mmol) and 23 mg of NCS in 8.0 mL anh. CH_3CN, 28 mg of **14** (90 %) were obtained as pale yellow oil. ^{1}H NMR $(CD_3)_2CO$, 300 MHz: δ = 5.72 (ddd, *J* = 4.50, 3.50, 0.90 Hz, 1 H, H_6), 4.96 (dm, *J* = 4.40 Hz, 1 H, H_1), 4.89 (m, 1 H, 5-H), 4.75 (m, 1 H, 3-H), 4.67 (m, 1 H, 2-H), 4.64 (s, 1 H, 8-H), 2.10 (s, 3 H, C*H*$_3$CO$_2$) ppm. ^{13}C NMR ($(CD_3)_2CO$, 75 MHz): δ = 170.55 (CH_3CO_2), 89.83 (C-5), 81.71 (C-1), 80.83 (C-3), 80.83 (C-6), 76.20 (C-2), 48.98 (C-8), 20.54 (*C*H$_3$CO$_2$) ppm. MS *m/z* 225 (M-2 + Na^+), 227 (M + Na^+). $C_8H_9ClO_4$ (205.6): calcd. C 46.96, H 4.43; found C 46.79, H 4.26.

Compound (15). From 28 mg of **10** (0.16 mmol) and 32 mg of NBS in 8.2 mL anh. CH_3CN, 35 mg of **15** (89 %) were obtained as pale yellow oil. ^{1}H RMN ($(CD_3)_2CO$, 300 MHz): δ = 5.71 (ddd, *J* = 4.40, 3.70, 0.90 Hz, 1 H, 6-H), 4.93 (dddd, *J* = 4.40, 2.60, 1.70, 0.90 Hz, 1 H, 1-H), 4.79 (m, 1 H, 5-H), 4.72 (m, 1 H, 3-H), 4.67 (dd, *J* = 4.40, 3.70 Hz, 1 H, 2-H), 4.60 (broad s, 1 H, 8-H), 2.11 (s, 3 H, C*H*$_3$CO$_2$) ppm. ^{13}C NMR ($(CD_3)_2CO$, 75 MHz): δ = 170.63 (CH_3CO_2), 89.37 (C-5), 81.04 (C-1), 80.84 (C-3), 80.23 (C-6), 75.14 (2-C), 57.89 (8-C), 20.03 (*C*H$_3$CO$_2$) ppm. IR ($CHCl_3$): ν = 2926, 1745, 1233 cm^{-1}. Anal. Calcd for $C_8H_9BrO_4$ (249.06): C, 38.58; H, 3.64. Found: C, 38.43; H, 3.49.

Compound (16). From 25 mg of **10** (0.15 mmol) and 31 mg of *p*-NO_2-C_6H_4-SCl in 7.3 mL anh. CH_3CN, 31 mg of **16** (48 %) were obtained as pale yellow oil. ^{1}H NMR **(**C_6D_6**,** 300 MHz**)**: δ = 7.66-7.60 (m, 2 H, Ar-H), 6.80-6.76 (m, 2 H, Ar-H), 4.27-4.13 (m, 3 H, 1-H, 3-H and 5-H), 4.01 (ddd, *J* = 6.80, 4.40, 0.90 Hz, 1 H, 6-H), 3.97 (broad s, 1 H, 8-H), 5.21 (m, 1 H, 2-H), 1.66 (s, 3 H, C*H*$_3$$CO_2$) ppm. ^{13}C NMR ($C_6D_6$, 75 MHz): δ = 171.20 ($CH_3$*C*$O_2$), 145.60 (Ar-C), 126.59 (2 x Ar-*C*H), 124.41 (2 x Ar-*C*H), 121.49 (Ar-C), 83.18, 81.53 and 78.69 (C-1, C-3 and C-5), 77.18 (C-6), 67.62 (C-2), 53.95 (C-8), 21.14 (*C*H_3CO_2) ppm. IR ($CHCl_3$): ν = 2923, 1740, 1319 cm^{-1}. MS m/z 346 (M + Na^+). Anal. Calcd for $C_{14}H_{13}NO_6S$ (323.05): C, 52.01; H, 4.05. Found C, 52.20; H, 4.33.

Compound (17). From 25 mg of **10** (0.15 mmol) and 31 mg of C_6H_5-SeCl in 7.3 mL anh. CH_3CN, 26 mg of **17** (55 %) were obtained as pale yellow oil. ^{1}H NMR (C_6D_6, 300 MHz): δ = 7.49-7.44 (m, 2 H, Ar-H), 6.97 - 6.90 (m, 3 H, Ar-H), 4.67 (ddd, *J* = 5.10, 1.60, 1.00 Hz, 1 H, 1-H), 4.37 (ddd, *J* = 4.40, 1.60, 1.00 Hz, 1 H, 5-H), 4.24 (ddd, *J* = 6.10, 4.40, 1.00 Hz, 1 H, 3-H), 4.15 (s, 1 H, 8-H), 4.02 (ddd, *J* = 6.10, 4.40, 1.00 Hz, 1 H, 6-H), 3.85 (ddd, *J* = 5.10, 4.40, 1.00 Hz, 1 H, 2-H), 1.59 (s, 3 H, C*H*$_3$$CO_2$) ppm. ^{13}C NMR ($C_6D_6$, 75 MHz): δ = 174.20 ($CH_3$*C*$O_2$), 133.27 (2 x Ar-*C*H), 129.73 (2 x Ar-*C*H), 127.53 (*C*H), 121.36 (Ar-*C*), 84.83 (C-5), 83.01 (C-1), 78.72 (C-3), 77.58 (C-6), 67.87 (C-2), 51.45 (C-8), 21.39 (*C*H_3CO_2) ppm. IR ($CHCl_3$): ν = 2953, 1727, 1399 cm^{-1}. MS m/z 349 (M + Na^+). Anal. Calcd for $C_{14}H_{14}O_4Se$ (326.01): C, 51.70; H, 4.34. Found: C, 51.53; H, 4.21.

Reaction of compound (10) with NIS

A solution of 25 mg of **10** (0.15 mmol) and 36 mg of NIS in 7.3 mL anh. CH_3CN was stirred during 24 h. at r.t. After this time the solvent was removed at vacuo and the reaction crude was purified by column chromatography (SiO_2, hexane:AcOEt, 7:3).

Compound (18). Yield, 15 mg (34 %). White solid. Mp 111-117 ºC. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 5.67 (ddd, *J* = 4.40, 3.70, 0.9 Hz, 1 H, 6-H), 5.09 (ddd, *J* = 4.40, 2.80, 1.60 Hz, 1 H, 5-H), 4.98 (dm, *J* = 4.40 Hz, 1 H, 1-H), 4.88 (dm, *J* = 4.40 Hz, 1 H, 3-H), 4.73 (dd, *J* = 4.40, 3.70 Hz, 1 H, 2-H), 4.62 (s, 1 H, 8-H), 2.17 (s, 3 H, C*H*$_3$$CO_2$) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 170.44 ($CH_3$*C*$O_2$), 90.65 (C-5), 82.84 (C-1), 80.76 (C-3), 80.61 (C-6), 75.66 (C-2), 24.51 (C-8), 20.04 (*C*H_3CO_2) ppm. IR ($CHCl_3$): ν = 2957, 2923, 2852, 1742, 1259, 1230, 1055, 797 cm^{-1}. MS m/z (%) 170 (M), 111 (10), 97 (18), 83 (18), 71 (31), 57 (55), 43 (100). Anal. Calcd for $C_8H_9IO_4$ (296.0): C, 32.45; H, 3.06. Found: C, 32.69; H, 3.24.

Compound (21). Yield, 25 mg (58 %). White solid. Mp 84-89 ºC. ^{1}H NMR (C_6D_6, 700 MHz): δ = 4.59 (dm, *J* = 5.10 Hz, 1 H, H-6), 4.43 (s, 1 H, H-7), 4.12 (dd, *J* = 6.30, 4.20 Hz, 1 H, H-2), 4.02 (d, *J* = 4.20 Hz, 1 H, H-1), 3.77 (dd, *J* = 6.30, 4.20 Hz, 1 H, H-4), 3.66 (dd, *J* = 5.10, 4.20 Hz, 1 H, H-5), 1.54 (s, 3 H, C*H*$_3$$CO_2$) ppm. ^{13}C NMR ($C_6D_6$, 175 MHz): δ = 120.50 ($CH_3$*C*$O_2$-), 85.82 (C-1), 83.94 (C-6), 78.03 (C-2), 76.25 (C-4), 67.43 (C-5), 28.31 (C-7), 20.87 (*C*H_3CO_2) ppm. IR ($CHCl_3$): ν = 2957, 2923, 2853, 1735, 1448, 1124, 1058, 860 cm^{-1}. MS m/z 319 (M + Na^+). Anal. Calcd for $C_8H_9IO_4$ (296.0): C, 32.45; H, 3.06. Found C, 32.61; H 3.19.

Reaction of compound (10) with m-CPBA

To a solution of 27 mg of **10** (0.16 mmol) in 1.6 mL CH_2Cl_2, 54 mg of m-CPBA (0.32 mmol) was added. The mixture was stirred at r.t. during 24 h. After this time the reaction crude was treated with 6 mL $NaHCO_3$ (5 %) and extracted with CH_2Cl_2 (5 x 10 mL). The organic extracts were dried with $MgSO_4$, filtered and the solvent was removed at vacuo affording 24 mg (89 %) of **19** as colourless oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 4.81 (dd, *J* = 7.25, 4.80 Hz, 1 H, H-6), 4.62 (d, *J* = 4.80 Hz, 1 H, H-5), 4.55 (d, *J* = 4.80 Hz, 1 H, H-1), 4.46 (dd, *J* = 7.25, 4.80 Hz, 1 H, H-7), 3.71 (d, *J* = 3.40 Hz, 1 H, H-2), 3.63 (d, *J* = 3.40 Hz, 1 H, H-4), 2.17 (s, 3 H, C*H*$_3$CO$_2$) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 171.48 (CH_3CO_2), 75.67 (C-1), 74.62 (C-5), 72.65 (C-6), 70.31 (C-7), 48.14, 48.04 (C-2, C-4), 20.04 (CH_3CO_2) ppm. IR ($CHCl_3$): ν = 34556, 2922, 2851, 1731, 1239, 861 cm^{-1}. MS m/z 209 (M + Na)$^+$. Anal. Calcd for $C_8H_{10}O_5$ (186.16): C, 51.61; H, 5.41. Found: C, 51.76; H, 5.54.

Synthesis of compounds (23-26). General procedure

To a solution of 1.0 eq. of **11** in 6.5 mL of acetonitrile, 1.1 eq. of the electrophilic reagent was added. The mixture was stirred under Ar at r.t. After the reaction time, the solvent was removed under reduced pressure and the crude product was purified by column chromatography (SiO_2, hexane: AcOEt 7:3).

Compound (23). From 25 mg of **11** (0.13 mmol) and 18 mg of NCS (0.14 mmol) in 6.3 mL anh. CH_3CN, after 9 days of reaction 20 mg of **23** (69 %) were obtained as pale yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 6.07 (ddd, *J* = 17.20, 10.20, 7.40 Hz, 1 H, C*H*=CH$_2$), 5.40 (dm, *J* = 17.20 Hz, 1 H, CH=C*H*$_{2trans}$), 5.38 (dm, *J* = 10.20 Hz, 1 H, CH=C*H*$_{2cis}$), 5.28 (d, *J* = 2.60 Hz, 1 H, H-5), 4.47 (d, *J* = 7.40 Hz, 1 H, H-4), 4.42 (m, 2 H, H-2, H-5a), 4.35 (s, 1 H, H-2a), 3.93 (dd, *J* = 10.50, 8.70 Hz, 1 H, C*H*$_2$Cl), 3.79 (dd, *J* = 10.50, 5.90 Hz, 1 H, C*H*$_2$Cl), 2.16 (s, 3 H, C*H*$_3$CO$_2$) ppm. ^{13}C NMR ($CDCl_3$, 75MHz): δ = 170.18 (CH_3CO_2), 132.89 (*C*H=CH$_2$), 120.99 (CH=*C*H$_2$), 83.70 (C-4), 82.41 (C-2 or C-5a), 79.63 (C-2a), 76.23, 75.99 (C-5, C-2 or C-5a), 40.21 (*C*H$_2$Cl), 20.85 (*C*H$_3$CO$_2$) ppm. IR ($CHCl_3$): ν = 2925, 2853, 1744, 1230, 1084, 1046, 737 cm^{-1}. MS m/z 255 (M + Na)$^+$. Anal. Calcd for $C_{10}H_{13}ClO_4$ (232.05): C, 51.62; H, 5.63. Found: C, 51.39; H, 5.38.

Compound (24). From 25 mg of **11** (0.13 mmol) and 35 mg of NBS (0.14 mmol) in 6.3 mL anh. CH_3CN, after 9 days of reaction 25 mg of **24** (72 %) were obtained as pale yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 6.08 (ddd, *J* = 17.20, 10.40, 7.50 Hz, 1 H, C*H*=CH$_2$), 5.40 (dm, *J* = 17.20 Hz, 1 H, CH=C*H*$_{2trans}$), 5.37 (dm, *J* = 10.40 Hz, 1 H, CH=C*H*$_{2cis}$), 5.29 (d, *J* = 2.60 Hz, 1 H, H-5), 4.57 (broad d, *J* = 7.60 Hz, 1 H, H-4), 4.46 (broad d, *J* = 2.60 Hz, 1 H, H-5a), 4.45 (dd, *J* = 8.70, 5.70 Hz, 1 H, H-2), 4.38 (s, 1 H, H-2a), 3.77 (dd, *J* = 9.90, 8.70 Hz, 1 H, C*H*$_2$Br), 3.61 (dd, *J* = 9.90, 5.70 Hz, 1 H, C*H*$_2$Br), 2.15 (s, 3 H, C*H*$_3$CO$_2$) ppm. ^{13}C NMR ($CDCl_3$, 75MHz): δ = 170.61 (CH_3CO_2), 133.32 (*C*H=CH$_2$), 121.49 (CH=*C*H$_2$), 84.14 (C-4), 82.68 (C-2 or C-5a), 80.30 (C-2a), 76.78, 76.67 (C-5, C-2 or C-5a), 28.59 (*C*H$_2$Br), 21.29 (*C*H$_3$CO$_2$) ppm. IR ($CHCl_3$): ν = 2920, 1743, 1230, 1087, 1043, 736 cm^{-1}. MS m/z 299 (M + Na)$^+$. Anal. Calcd for $C_{10}H_{13}BrO_4$ (276.00): C, 43.44; H, 4.73. Found: C, 43.51; H, 4.97.

Compound (25). From 25 mg of **11** (0.13 mmol) and 32 mg of NIS (0.14 mmol) in 6.5 mL anh. CH_3CN, after 6 days of reaction 30 mg of **25** (73 %) were obtained as pale yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 6.10 (ddd, *J* = 17.20, 10.30, 7.50 Hz, 1 H, C*H*=CH_2), 5.38 (ddd, *J* = 17.20, 1.50, 0.90 Hz, 1 H, CH=CH_{2trans}), 5.37 (ddd, *J* = 10.30, 1.50, 0.90 Hz, 1 H, CH=CH_{2cis}), 5.29 (d, *J* = 2.70 Hz, 1 H, H-5), 4.56 (d, *J* = 7.50 Hz, 1 H, H-4), 4.49 (dd, *J* = 9.00, 5.70 Hz, 1 H, H-2), 4.48 (d, *J* = 2.70, 1 H, Hz H-5a), 4.47 (s, 1 H, H-2a), 3.56 (dd, *J* = 9.90, 9.00 Hz, 1 H, CH_2I), 3.42 (dd, *J* = 9.90, 5.70 Hz, 1 H, CH_2I), 2.15 (s, 3 H, CH_3CO_2) ppm. ^{13}C NMR ($CDCl_3$, 75MHz): δ = 170.55 (CH_3CO_2), 133.36 (*C*H=CH_2), 121.45 (CH=*C*H_2), 84.12 (C-4), 83.17 (C-2), 80.66 (C-2a), 77.09, 77.7 (C-5, C-5a), 28.59 (*C*H_2Br), 21.23 (*C*H_3CO_2), 1.82 (*C*H_2I) ppm IR ($CHCl_3$): ν = 2929, 2851, 1744, 1232, 1047 cm^{-1}. MS m/z 347 $(M + Na)^+$. Anal. Calcd for $C_{10}H_{13}IO_4$ (323.99): C, 37.06; H, 4.04. Found: C, 37.31; H, 4.29.

Compound (26). From 30 mg of **11** (0.15 mmol) and 32 mg *p*-NO_2-C_6H_4-SCl (0.17 mmol) in 7.6 mL anh. CH_3CN, after 9 days of reaction 17 mg of **26** (32 %) were obtained as pale yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 8.11-8.05 (m, 2 H, 2 x C*H*Ar), 7.38-7.32 (m, 2 H, 2 x C*H*Ar), 6.07 (ddd, *J* = 17.30, 10.50, 7.70 Hz, 1 H, C*H*=CH_2), 5.36 (dm, *J* = 17.30 Hz, 1 H, CH=CH_{2trans}), 5.33 (dm, *J* = 10.50 Hz, 1 H, CH=CH_{2cis}), 5.19 (d, *J* = 2.50 Hz, 1 H, H-5), 4.51 (broad d, *J* = 7.70 Hz, 1 H, H-4), 4.29 (dd, *J* = 8.80, 5.90 Hz, 1 H, H-2), 4.28 (s, 1 H, H-2a), 4.24 (d, *J* = 2.50 Hz, 1 H, H-5a), 3.48 (dd, *J* = 13.60, 8.80 Hz, 1 H, CH_2-S), 3.38 (dd, *J* = 13.60, 5.90 Hz, 1 H, CH_2-S), 2.04 (s, 3 H, CH_3CO_2) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 170.68 (*C*H_3CO_2), 146.92 (S-*C*Ar), 145.57 (*C*Ar-NO_2), 133.41 (*C*H=CH_2), 126.93 (2 x *C*HAr), 124.50 (2 x *C*HAr), 121.53 (CH=*C*H_2), 84.94 (C-4), 81.78, 80.00, 77.61 (C-2, C-2a, C-5a), 76.74 (C-5), 30.52 (*C*H_2S), 21.33 (*C*H_3COO) ppm. IR ($CHCl_3$): ν = 3100, 2925, 2854, 1745, 1595, 1341, 1188, 1092, 991 cm^{-1}. MS m/z 374 $(M + Na)^+$. Anal. Calcd for $C_{16}H_{17}NO_6S$ (351.08): C, 54.69; H 4.88. Found: C, 54.93; H, 5.12

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