Oxidative cyclization of γ-alkylidene butenolides. Stereoselective preparation of spirolactones

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Abstract
A new route to 1,6-dioxaspiro[4.4]non-3-en-2-ones is established by bromoetherification of dihydroxybutenolides. An asymmetric total synthesis of 8-*epi*-crassalactone D starting from methyl cinnamate has been accomplished.

Keywords: γ-Spirolactones, oxidative cyclization, stereoselective synthesis, crassalactones, bromoetherification

Introduction

Spiro-γ-lactones constitute an important class of oxygen-containing heterocyclic compounds, and such groups can be found in many biologically active natural products.[1] Among them, the 1,6-dioxaspiro[4.4]non-3-en-2-ones constitute a family that have attracted our attention very recently due to their structural originality and biological activity. For example, the styryl-lactone (+)-crassalactone D (**1a**, Figure 1) has recently been isolated from an extract of the leaves and twigs of *Polyalthia crassa* Parker (Annonaceae), and its structure was determined on the basis of spectroscopic methods. Single-crystal X-ray analysis and the Mosher ester method were used to confirm its absolute stereochemistry. Spirolactone **1a** showed broad cytotoxic activity against murine lymphocytic leukemia, human colon, nasopharyngeal, lung and breast carcinomas.[2] Pyrenolide D **2**, however, was isolated from the phytopathogenic fungus *Pyrenophora teres* (Diedicke) Drechsler (FO 7508),[3] and its absolute configuration was determined by pioneer synthetic work in this field.[4] Although **2,** like other pyrenolides, was not active against fungi, it was found to be cytotoxic toward HL-60 cells at IC_{50} 4 μg/ml.

(+)-Massarinolin A **3** is a bioactive sesquiterpenoid isolated by Gloer *et al*. from liquid cultures of the aquatic fungus *Massarina tunicata* Shearer & Fallah.[5] It shows biological activity against *Bacillus subtilis* (ATCC 6501) and *Staphylococcus aureus* (ATCC 29213). It appears to be biosynthesized from a farnesyl-type precursor and even though its relative stereochemistry

was deduced by spectroscopic methods its absolute stereochemistry remains a challenge for synthetic chemists. The ring system found in compound **3** has previously been encountered only in expansolides A and B (**4**, and **5**), reported as metabolites of *Penicillium expansum*.[6] Their absolute configuration was established using the modified Mosher method.[7]

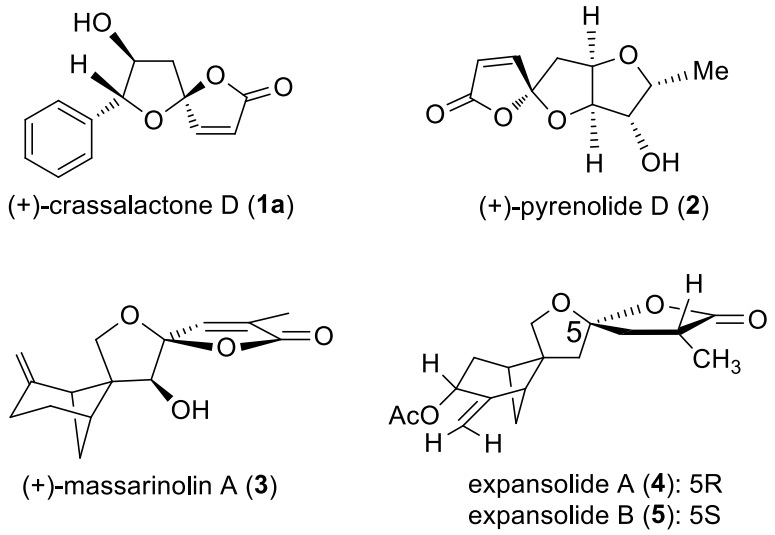


Figure 1. Biologically active spiro γ-lactones.

Although pioneer synthetic approaches to spirobutenolides have been reviewed by Knight in 1994,[8] further synthetic efforts in this topic have been reported.[9] The first total synthesis of (+)-pyrenolide D **2** started from tri-*O*-acetyl-D-galactal and was reported by Gin *et al.* in 2001. This pioneer synthetic work led to the absolute stereochemical assignment of **2**.[10] The enantiospecific synthesis of four hydroxylated analogues of **2** was reported by Robertson *et al*.[11] This synthetic approach started from D-glucose and was based on furan oxidative spirocyclization. Shortly afterwards, Vassilikogiannakis *et al*. reported the photooxygenation of 2-(γ-hydroxyalkyl)furans as a newly developed technology applied to the synthesis of γ-spiroketal γ-lactones such as (+)-crassalactone D (**1a**), and three different epimers of pyrenolide D, **2**.[12] The asymmetric total synthesis of (+)-crassalactone D from the commercially available 3-bromo-1-phenyl-1-propene was published by Yang *et al*. in 2009. Their successful synthesis was elegantly achieved by employing an oxidative spirocyclization of a dihydroxylated 2-substituted furan as the key step. Two close analogues of (+)-crassalactone D **1a**, have also been prepared in the course of the synthetic work.[13]

Results and Discussion

In order to test whether the bromoetherification of hydroxybutenolides might afford an efficient way towards the synthesis of 1,6-dioxaspiro[4.4]non-3-en-2-ones of the type **1a**, we decided to

study the stereochemical outcome of the oxidative cyclization reaction of 7-*epi*-goniobutenolides A and B. (Figure 2)

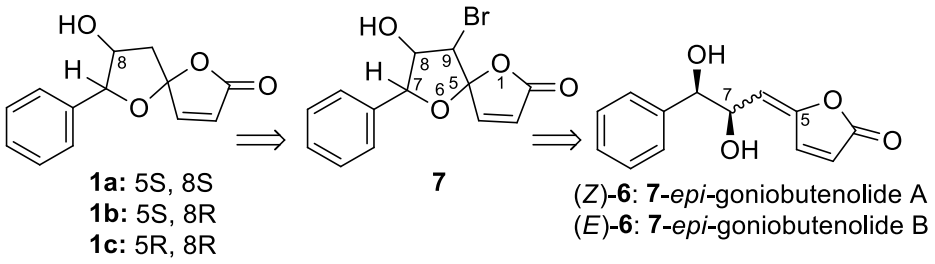
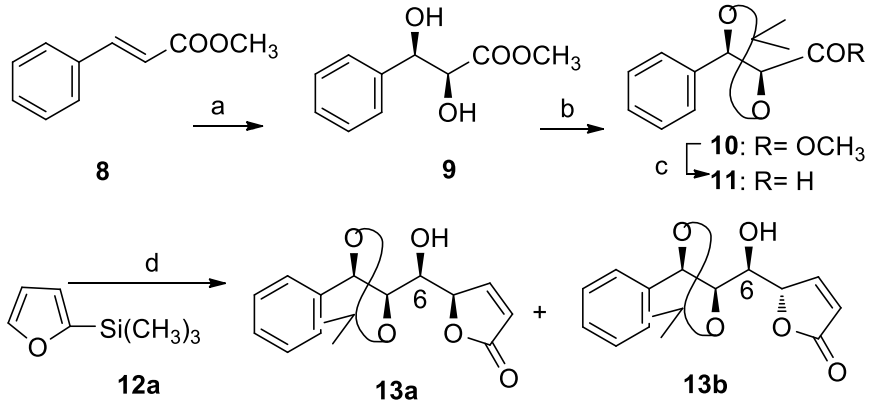


Figure 2. Retrosynthetic analysis of crassalactones.

The preparation of both stereoisomers of 7-*epi*-goniobutenolide **6** was accomplished by following pioneer synthetic work in this field.[14] Isolation of the aldehyde **11** afforded the opportunity to assay the vinylogous Mukaiyama aldol reaction using the 2-silyloxyfuran **12a** (TMSOF) in the presence of Lewis acids such as $TiCl_4$ or $SnCl_4$.[15] The reaction yielded a mixture of stereoisomers **13a** and **13b** with similar results (72% yield and a moderate stereoselectivity, favouring the *threo* adduct **13a**: **13b** = 1.7: 1) (Scheme 1).



a) ADmix-β, $CH_3SO_2NH_2$, tBuOH/H_2O, rt (87%). b) $(CH_3)_2C(OCH_3)_2$, *p*-TsOH, CH_2Cl_2 (90%) c) DIBALH, -78 ºC (94%) d) $TiCl_4$ or $SnCl_4$, diethyl ether, -78 ºC (72%).

Scheme1. Vinylogous aldol reaction on cinnamyl aldehyde derivatives.

A possible explanation for the preference towards **13a** may lie in hydrogen bonding formation between the hydroxy function and the lactone oxy group (see Figure 3).[16] The stereo-selective formation of **13a** in the vinylogous Mukaiyama aldol reaction led us to undertake computational studies with a view to determining the the relative stability of both isomers : **13a** and **13b**. After a conformational search performed with MM2 , the lower energy conformer **13a**

was found to be 4.63 kcal/mol more stable than **13b**. Additionally, the hydrogen bonding formation for **13a**, for a O-H distance of d: 2.269 Å, was seen to be more feasible in comparison with the value of d: 3.872 Å obtained for the same O-H distance in **13b**.

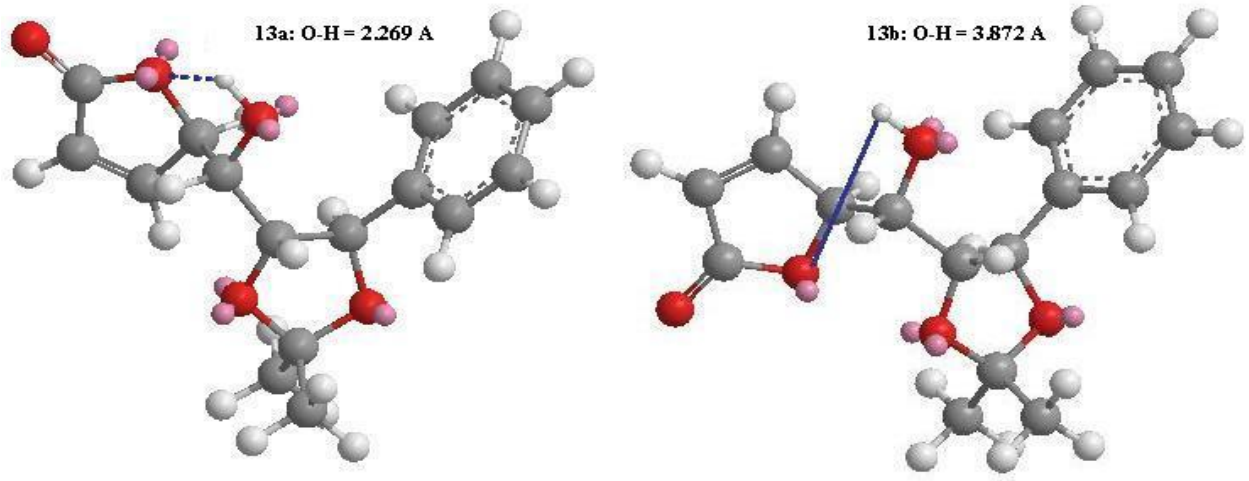
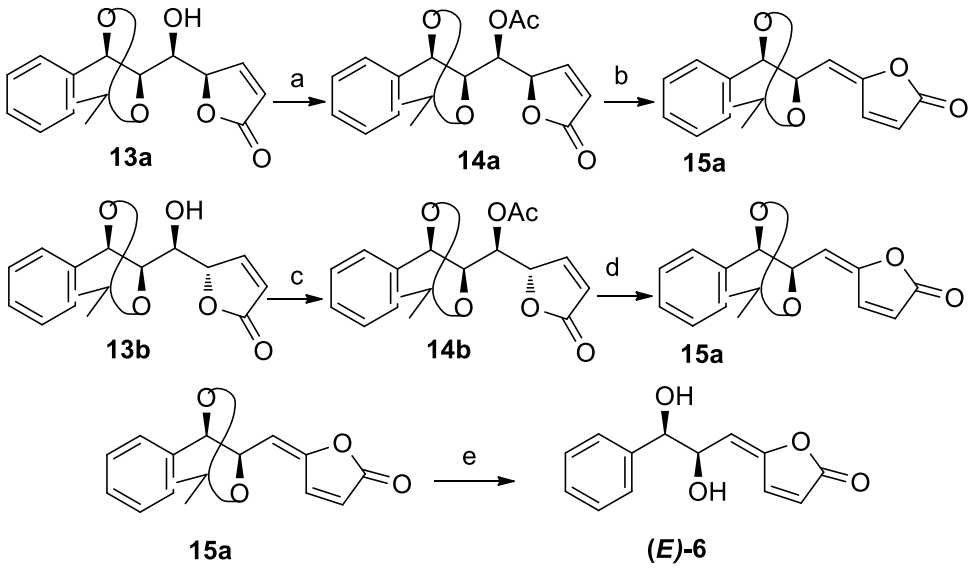


Figure 3. MM2 calculations for **13a** and **13b** structures.

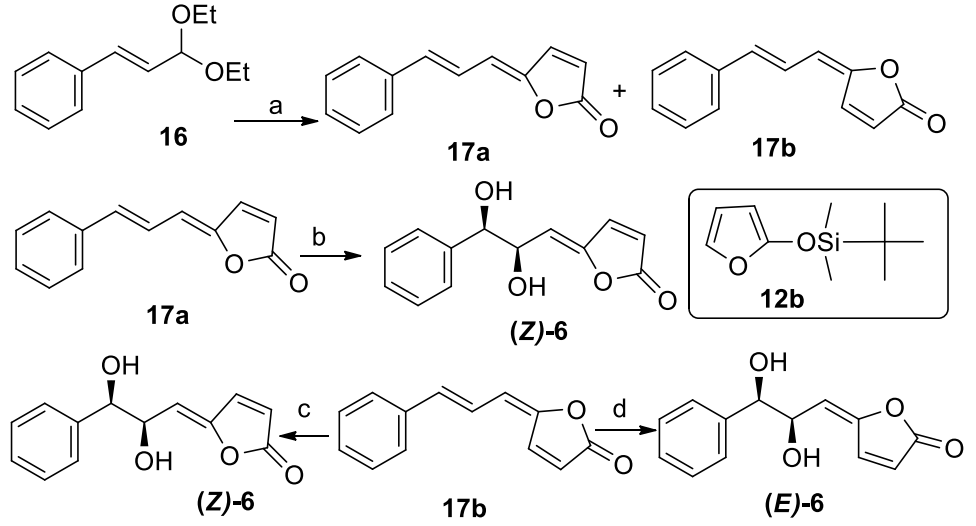
Elimination of the hydroxyl function on C-6 in both isomers **13a** and **13b** required the transformation into the corresponding acetates (**14a** and **14b**) and further treatment with base (Scheme 2). Treatment of **13b** with acetic anhydride in pyridine led to the isolation of acetate **14b** in 82% yield. Elimination of the acetate was accomplished by treatment with DBU and allowed us to isolate the butenolide **15a** in quantitative yield. In the case of **13a**, however, the use of dimethylaminopyridine (DMAP) to obtain the acetate **14a** was necessary. The reluctance of the hydroxyl function to undergo the transformation into the acetate in this case may be due to the above-mentioned formation of hydrogen bonding with the lactone oxy function. Chromatographic separation of the crude product on silica gel led to the recovery of the starting material, and the desired product, **14a**, with 25% and 68% yields respectively. Treatment of **14a** with DBU led to the elimination product **15a**, with 65% yield. It is known that this elimination takes place through an E_1cb mechanism, and we assume that the convergent stereoselectivity obtained in both cases would mostly be due to stereoelectronic factors, which may be explained in terms of electronic repulsion between the lactone oxygen lone pairs and those of acetonide functionality, working on an identical intermediate.[17]

The deprotection of acetonide **15a** took place smoothly without epimerization by treatment with *p*-toluenesulfonic acid in methanol and we were able to isolate the 7-*epi*-goniobutenolide (*E*)-**6** in 73% yield.



a) Ac_2O, pyr, DMAP, CH_2Cl_2 (68%). b) DBU (65%). c) Ac_2O, pyr, CH_2Cl_2 (82%). d) DBU (100%) e) *p*-TsOH, MeOH (73%).

Scheme 2. Synthesis of butenolide (*E*)-**6**.



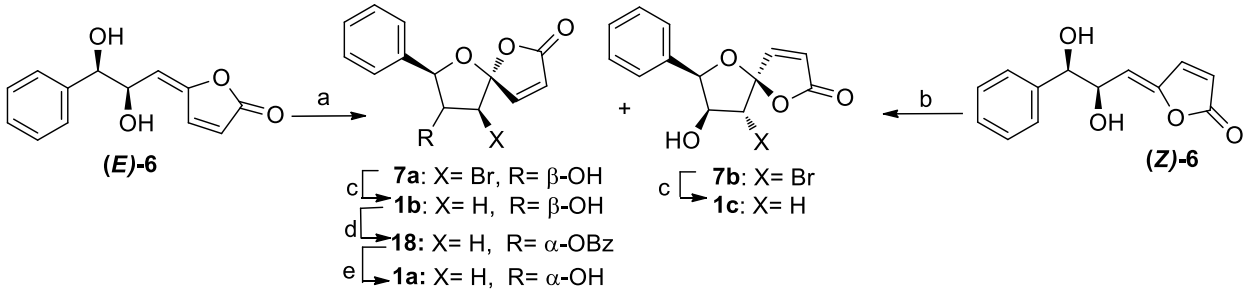
a) **12b**, $TiCl_4$ then KOAc, AcOH. b) ADmix-β, 0 ºC or rt. c) ADmix-β 24 h, rt (82%). d) ADmix-β 24 h, 0 ºC (80%).

Scheme 3. Asymmetric synthesis of butenolides (*Z*)- and (*E*)-**6**.

Access to both isomers **13a** and **13b** was achieved following a modified previously-reported procedure[14c] starting from the cinnamyl aldehyde diethyl acetal **16** (Scheme 3). The trienes **17a** and **17b** were obtained at a 1: 1 ratio in 87% combined yield. The *E*- and *Z*- isomers, whose stereochemistry was established by NOE experiments, were readily separated by flash

chromatography. The dihydroxylation of **17a** under standard conditions afforded (*Z*)-**6** in 85% yield and 98% ee. The other isomer **17b**, however, yielded either isomer (*Z*)-**6** or (*E*)-**6** depending on the reaction temperature, in both cases with high yields (82% and 80%, respectively). The formation of (Z)-**6** took place when the reaction was performed at room temperature and can be explained in terms of isomerisation occurring under the reaction conditions and concomitant formation of a hydrogen bonding between the hydroxyl function on C-6 and the furanone oxy function which renders this stereoisomer more stable.

With both stereoisomers in our hands (*E*)- and (*Z*)-**6**, we were ready to study the spirocyclization under oxidative conditions and establish the stereochemical outcome of the cyclization process (Scheme 4). Treatment of both isomers (*E*)- and (*Z*)-**6** with N-bromo-succinimide and sodium bicarbonate in chloroform at 0 ºC afforded the same mixture of hydroxybromolactones, **7a**: **7b** = 3:1, in moderate yields (62% and 65%, respectively).[19]



a) NBS, $NaHCO_3$, 0 ºC, 48h (70%). b) NBS, $NaHCO_3$, 0 ºC, 72h (55%). c) nBu_3SnH, AIBN,(100%). d) Ph_3P, DEAD, BzOH, (75%). e) Ref. 13.

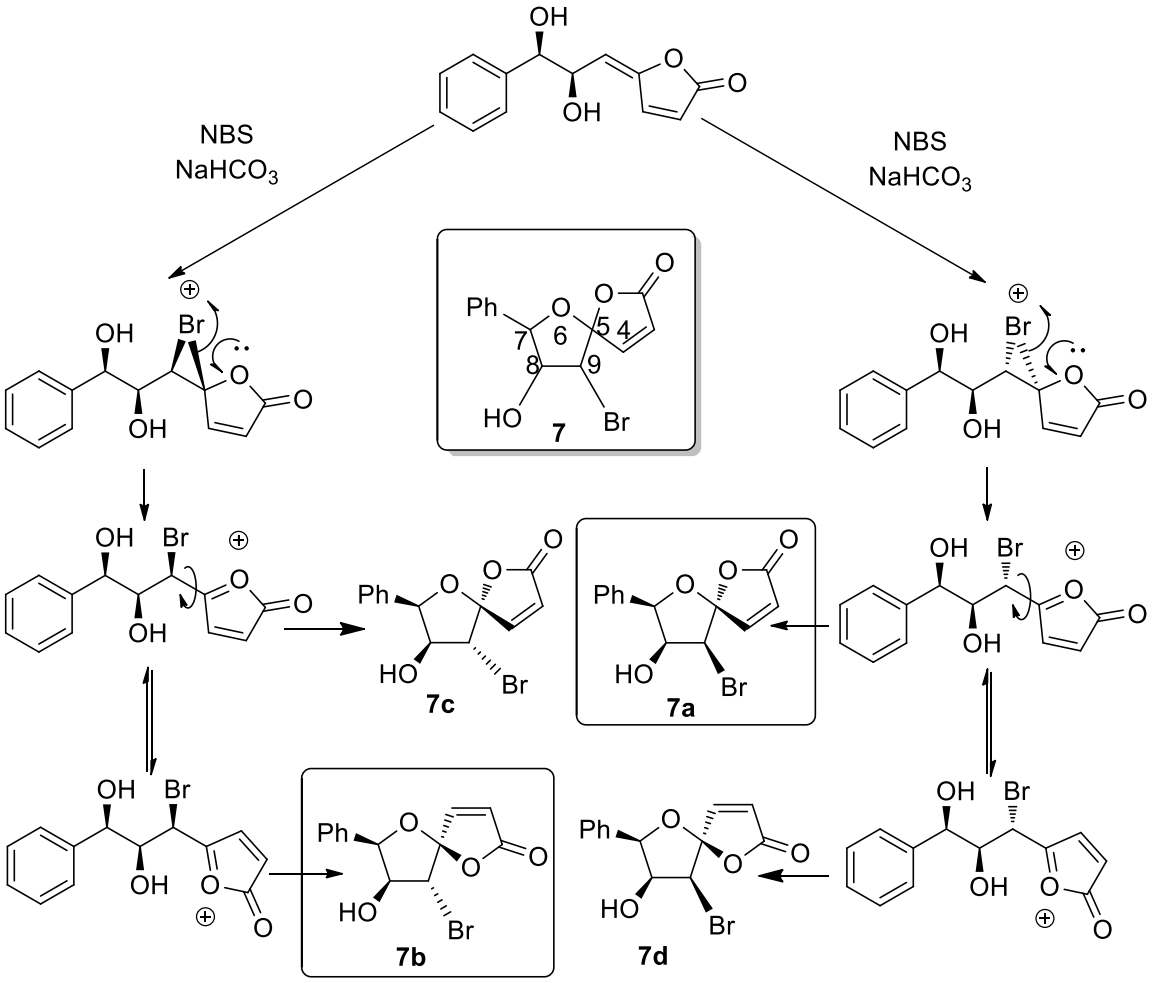
Scheme 4. Oxidative cyclization of dihydroxy butenolides.

The reaction mixture proved to be chromatographically unresolvable on a flash column of silica gel. However, the structural assignment was possible by full spectroscopic analysis of the reaction mixture, which included COSY, ROESY, HMQC and HMBC spectra.

Structural assignment of **7a** was based on the multiplicity found for the hydrogen atoms on C9 at δ= 4.82ppm (d, J = 4 Hz), C8 at δ = 4.62 ppm (dd, $J_1 = J_2 = 4$ Hz), and C7 at δ = 5.51 ppm (d, J = 4 Hz), which suggests the *cis* stereochemistry for the three hydrogen atoms (Scheme 5). Additionally, the absence of correlation between the protons at C9 and C4 suggests the *trans* stereochemistry between the bromo and the lactone oxy functions. In the case of **7b**, however, the hydrogen at C9 appears as a singlet centered at δ = 4.48 ppm, which suggests the *trans* stereochemistry with respect to the OH function on C8. Again, the absence of correlation between the protons at C9 and C4 suggests the *trans* relationship between the bromine and the lactone oxygen.

From a mechanistic point of view, the formation of **7a** and **7b** with the exclusion of **7d** and **7c** respectively obeys the stereoelectronic effect that is developed at the transition state of the

bromoetherification reaction: the electronic repulsion between the electronic lone pairs on the bromine and the lactone oxygen.



Scheme 5. Mechanism of formation of the spirobutenolides **7a** and **7b**.

The formation of bromolactone **7a** as the major isomer of the reaction mixture with respect to **7b** can mainly be assigned to a stereoelectronic effect (Figure 4).[20] Although the cyclization via *antiperiplanar* attack through the transition state **TS-2** should be easier than that with the *synclinal* orientation (**TS-1**), the strong steric hindrance developed between the bromine atom and the C4-C5 bond of the furanone nucleus in **TS-2** helps to rationalise the formation of the major isomer **7a** from **TS-1** , which is much less sterically hindered.

Treatment of the bromolactones **7a** and **7b** with tri-n-butyltin hydride in refluxing toluene afforded the 8-*epi*-crassalactone D **1b**, and 5,8-*epi*-crassalactone D **1c**, in quantitative yields. The hydroxyspirolactones **1b** and **1c** were obtained at the same (3:1) ratio and were separated by flash chromatography on silica gel. Treatment of **1b** under Mitsunobu conditions[21] led to the isolation of the benzoate **18** with 75% yield. Since the transformation of the benzoate **18** into

(+)-crassalactone D **1a**, has been recently accomplished by Yang *et al*,[13] our present contribution may also be considered as a formal total synthesis of the biologically active compound.

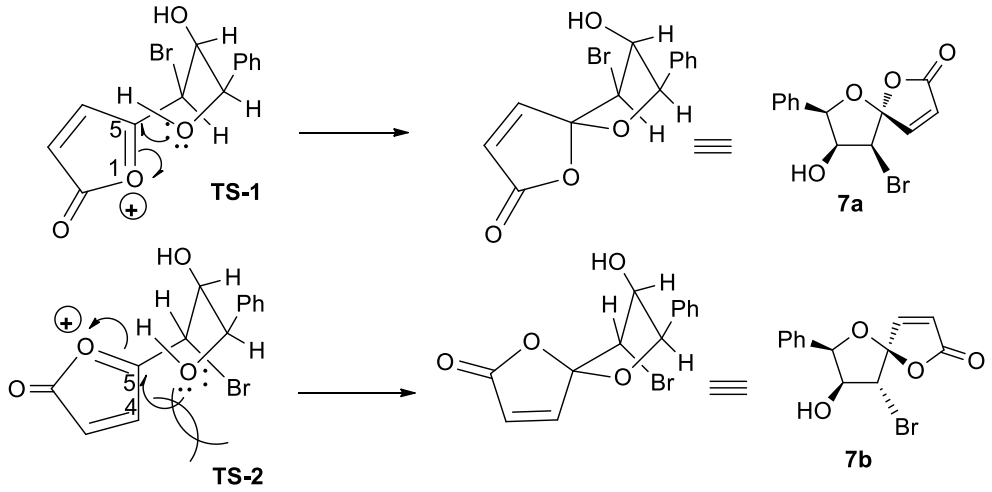


Figure 4. Stereoselective formation of **7a**.

Conclusions

In summary: we have developed a new route to 1,6-dioxaspiro[4.4]non-3-en-2-ones through the oxidative cyclization of hydroxybutenolides. The bromoetherification reaction of 7-*epi*-goniobutenolides **A** [(*Z*)-**6]** and **B** [(*E*)-**6]** afforded a mixture of bromospirolactones **7a** and **7b** in a 3:1 ratio, which was reduced by tributyltin hydride to afford the target molecules **1b** and **1c**. After chromatographic separation of the reaction mixture, the stereochemical outcome of the cyclisation reaction was elucidated by full spectroscopic analysis.

Experimental Section

General. 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 indicated otherwise. IR spectra were recorded for samples in $CHCl_3$ solution on NaCl plates, unless otherwise stated, with an FT-IR instrument. HRMS determinations (EI) were recorded at the Mass Spectrometry Service of the University of Salamanca, Spain. Microanalyses were performed on a Perkin-Elmer 240-B analyzer**.**

All reactions were conducted under a positive pressure of argon, utilizing standard bench-top techniques for handling of air-sensitive materials. Chemicals and solvents were obtained from commercial sources and used as received with the exception of benzene, toluene and dioxane

which were distilled from sodium and benzophenone. Yields reported are for chromatographic pure isolated products unless stated otherwise.

(2*S*,3*R*)-Methyl 2,3-dihydroxy-3-phenylpropanoate (9). Methyl *trans*-cinnamate **8** (2.17 g, 13.38 mmol) was added to a solution of ADmix-β (18.73 g) and $CH_3SO_2NH_2$ (1.27 g, 13.38 mmol) in H_2O/tBuOH (100 mL, 1:1). The reaction mixture was stirred for 14 hours at room temperature. Then Na_2SO_3 (12 mL, 0.5 M) was added and the mixture was stirred for an additional hour. The reaction mixture was extracted with ethyl acetate, and the combined organics layers were washed with brine and dried over anhydrous Na_2SO_4, and the solvent was evaporated under reduced pressure. The crude product was purified by flash chromatography, using hexane/Ethyl acetate (1:1) as eluent, to afford 9 (2.29 g, 87%) as a white solid. Mp 125-127 ºC. $[\alpha]_D^{20}$: -10.06 (c 0.75, $CHCl_3$).^{1}H NMR ($CDCl_3$): δ 3.67 (s, 3H), 4.26 (d, 1H, *J* 3.2 Hz), 4.92 (d, 1H, *J* 3.2 Hz), 7.26-7.34 (m, 5H) ppm. ^{13}C NMR ($CDCl_3$): δ 52.8 (q), 74.7 (d), 75.3 (d), 126.5 (2C, d), 128.1 (d), 128.5 (2C, d), 140.3 (s), 173.4 (s) ppm. IR: ν_{max} = 3525, 3051, 2982, 1737, 1263 cm^{-1}. HRMS-EI (M++Na): Calculated for $C_{10}H_{12}O_4Na$: 219.0627, experimental: 219.0642.

The ee value (99%) of the diol ester **9** was determined by direct HPLC analysis on a Chiralcel OJ column: 10% CH_3CN/H_2O, 0.8 mL/min, (2S, 3R) 11.1 min, (2R, 3S) 14.9 min.

Methyl (4*S*,5*R*)-2,2-dimethyl-5-phenyl-1,3-dioxolane-4-carboxylate (10). A catalytic amount of *p*-toluenesulfonic acid was added to a solution of **9** (3.83 g, 19.5 mmol) and 2,2-dimethoxypropane (4.8 mL, 39.04 mmol) in 100 mL of CH_2Cl_2. The reaction mixture was stirred for 3 hours at room temperature. Then, 20 mL of a saturated aqueous solution of $NaHCO_3$ was added and the mixture was stirred for 15 minutes. The mixture was extracted with CH_2Cl_2, the combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and the organic solvent was evaporated off under reduced pressured to afford **10** (4.14 g, 90%) as a yellow oil. $[\alpha]_D^{20}$: +22.3 (c 2.09, $CHCl_3$). ^{1}HNMR ($CDCl_3$): δ 1.56 (s, 3H), 1.62 (s, 3H), 3.79 (s, 3H), 4.34 (d, 1H, *J* 7.8 Hz), 5.15 (d, 1H, *J* 7.8 Hz), 7.35-7.42 (m, 5H) ppm. ^{13}CNMR ($CDCl_3$): δ 26.0 (q), 27.1 (q), 52.5 (q), 80.9 (d), 81.4 (d), 111.8 (s), 126.7 (2C, d), 128.7 (d), 128.8 (2C, d), 137.9 (s), 170.9 (s) ppm. IR: νmax 3424, 3056, 2988, 2930, 1731, 1265 cm^{-1}. Analc. Calc. for $C_{13}H_{16}O_4$: C, 66.09. H, 6.83, O, 27.09. Found: C, 66.13. H, 6.80, O, 27.07.

(4*S*,5*R*)-2,2-Dimethyl-5-phenyl-1,3-dioxolane-4-carbaldehyde (11). Diisobutylaluminum hydride (17.84 mL, 1M in toluene) was added to a solution of **10** (2.81 g, 11.89 mmol) in dry toluene (50 mL) at -78 ºC and under strict argon atmosphere. The reaction mixture was stirred for five hours at the same temperature. Then, 5 mL of MeOH and 50 mL of 1M HCl were added. The mixture was stirred 30 minutes at 0 ºC, after which it was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and the organic solvent was evaporated off under reduced pressure. The crude residue was purified by flash chromatography using hexane/ethyl acetate (6:4) as eluent, to afford **11** (2.30 g, 94%) as a yellow oil. $[\alpha]_D^{20}$: -22.86 (c 1.12, $CHCl_3$). ^{1}HNMR ($CDCl_3$): δ 1.52 (s, 3H), 1.61 (s, 3H), 4.18 (dd, 1H, J_1 7.8 Hz, J_2 1.8 Hz), 5.06 (d, 1H, *J* 7.8 Hz), 7.33-7.41 (m, 5H), 9.79 (d, 1H, *J* 1.8 Hz)

ppm. ^{13}CNMR ($CDCl_3$): δ 26.3 (q), 27.00 (q), 78.7 (d), 86.8 (d), 111.8 (s), 126.4 (2C, d), 128.7 (d), 128.9 (2C, d), 137.7 (s), 200.3 (d) ppm. IR: νmax 3444, 2983, 2926, 1733, 1063 cm^{-1}. Analc. Calc. for $C_{12}H_{14}O_3$: C, 69.88. H, 6.84. O, 23.27. Found: C, 69.90. H, 6.87. O, 23.22.

(R)-5-((S)-((4R,5R)-2,2-dimethyl-5-phenyl-1,3-dioxolan-4-yl)(hydroxy)methyl)furan-2(5H)-one (13a) and (S)-5-((S)-((4R,5R)-2,2-dimethyl-5-phenyl-1,3-dioxolan-4-yl)(hydroxy) methyl)furan-2(5H)-one (13b). Tin tetrachloride (5.94 mL, 1M in dichloromethane) was added to a solution of **11** (815.2 mg, 3.96 mmol) in freshly distilled diethyl ether (30 mL) at -78 ºC under argon atmosphere. The reaction mixture was stirred for 15 min. and then, trimethylsilyloxyfuran **12a**[15] (783.5 mg, 3.96 mmol) was added. The reaction mixture was stirred for 3 hours at the same temperature after which 20 mL of a saturated aqueous solution of $NaHCO_3$ were added. The mixture was warmed to room temperature and the aqueous layer was extracted with ethyl ether. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude residue was fraccionated by flash chromatography, using hexane/ethyl acetate (1:1) as eluent, to afford **13a** (514.1 mg, 46%) as a white solid and **13b** (288.9 mg, 27%) as a yellow oil.

13a. White solid Mp172-174 ºC. $[\alpha]_D^{20}$: -44.5 (c = 0.85, $CHCl_3$). ^{1}HNMR ($CDCl_3$): δ 1.48 (s, 3H), 1.55 (s, 3H), 2.65 (d, 1H, *J* 4.0 Hz), 3.84 (ddd, 1H, J_1 8.4 Hz, J_2 8.0 Hz, J_3 4.0 Hz), 4.00 (dd, 1H, J_1 8.4 Hz, J_2 7.5 Hz), 5.02 (d, 1H, *J* 7.5 Hz), 5.17 (m, 1H), 6.04 (dd, 1H, J_1 5.7 Hz, J_2 2.0 Hz), 7.26-7.31 (m, 3H), 7.37 (dd, 1H, J_1 5.7 Hz, J_2 1.6 Hz), 7.42-7.44 (m, 2H) ppm. ^{13}CNMR ($CDCl_3$): δ 26.9 (q), 27.2 (q), 73.8 (d), 81.9 (d), 82.3 (d), 84.1 (d), 110.0 (s), 122.2 (d), 127.3 (2C, d), 128.2 (d), 128.3 (2C, d), 138.4 (s), 153.9 (d), 172.8 (s) ppm. IR: νmax 3395, 2988, 1736, 1052 cm^{-1}. HRMS-EI (M++Na): Calculated for $C_{16}H_{18}O_5Na$: 313.1046, experimental: 313.1039.

13b. Yellow oil. $[\alpha]_D^{20}$: +89.7 (c 0.725, $CHCl_3$). ^{1}HNMR ($CDCl_3$): δ 1.52 (s, 3H), 1.55 (s, 3H), 3.01 (d, 1H, *J* 4.5 Hz), 3.96 (dd, 1H, J_1 7.5 Hz, J_2 6.8 Hz), 4.07 (m, 1H), 5.06 (d, 1H, *J* 7.5 Hz), 5.21 (m, 1H), 6.11 (dd, 1H, J_1 5.8 Hz, J_2 2.0 Hz), 7.30-7.45 (m, 5H), 7.54 (dd, 1H, J_1 5.8 Hz, J_2 1.4 Hz) ppm. ^{13}CNMR (CDCl3): δ 27.0 (q), 27.1 (q), 72.1 (d), 81.2 (d), 82.5 (d), 83.3 (d), 110.0 (s), 122.7 (d), 127.0 (2C, d), 128.4 (d), 128.5 (2C, d), 137.9 (s), 153.8 (d), 173.0 (s) ppm. IR: νmax 3395, 2988, 1736, 1052 cm^{-1} HRMS-EI (M++Na): Calculated for $C_{16}H_{18}O_5Na$: 313.1046, experimental: 313.1048.

(S)-((4S,5R)-2,2-Dimethyl-5-phenyl-1,3-dioxolan-4-yl)((R)-5-oxo-2,5-dihydrofuran-2-yl) methyl acetate (14a). Acetic anhydride (139 μL, 1.4 mmol) was added to a solution of **13a** (368.3 mg, 1.27 mmol), pyridine (150 μL, 1.5 mmol) and a catalytic amount of DMAP in 4 mL of CH_2Cl_2 at room temperature. The reaction mixture was stirred for 2 hours after which crushed ice was added. The mixture was stirred for an additional hour and extracted with ethyl ether. The combined organic layers were washed successively with 1M HCl, a saturated aqueous solution of $NaHCO_3$, brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude residue was purified by flash chromatography, using hexane/Ethyl acetate (1:1) as eluent, to afford **14a** (0.86 mmol, 68%) as a yellow oil. $[\alpha]_D^{20}$: -84.4 (c = 1.25, $CHCl_3$). ^{1}HNMR ($CDCl_3$): δ 1.45 (s, 3H), 1.51 (s, 3H), 1.52 (s, 3H), 4.18 (dd, 1H, J_1 9.2 Hz, J_2 7.8 Hz), 4.68 (d,

1H, *J* 7.8 Hz), 5.19 (dd, 1H, J_1 9.2 Hz, J_2 2.2 Hz), 5.37 (dd, 1H, J_1 4.0 Hz, J_2 2.2 Hz), 6.00 (dd, 1H, J_1 5.8 Hz, J_2 2.2 Hz), 7.24-7.29 (m, 6H) ppm. ^{13}CNMR ($CDCl_3$): δ 20.4 (q), 27.1 (q), 27.4 (q), 71.4 (d), 79.6 (d), 82.1 (d), 83.1 (d), 110.3 (s), 122.8 (d), 127.6 (2C, d), 128.7 (2C, d), 128.9 (d), 137.1 (s), 152.7 (d), 170.0 (s), 172.5 (s) ppm. IR: νmax 3054, 2987, 1751, 1265, 1226, 738 cm^{-1}. HRMS-EI (M++Na): Calculated for $C_{18}H_{20}O_6Na$: 355.1152, experimental: 355.1161.

(S)-((4S,5R)-2,2-Dimethyl-5-phenyl-1,3-dioxolan-4-yl)((S)-5-oxo-2,5-dihydrofuran-2-yl) methyl acetate (14b). Acetic anhydride (65 μL, 0.65 mmol) was added to a solution of **13b** (126.5 mg, 0.44 mmol) and pyridine (60 μL, 0.872 mmol) in 5 mL of CH_2Cl_2 at room temperature. The reaction mixture was stirred for 12 hours, after which crushed ice was added. The mixture was stirred for an additional hour and extracted with ethyl ether. The combined organic layers were washed successively with 1M HCl, a saturated aqueous solution of $NaHCO_3$, brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude residue was purified by flash chromatography, using hexane/ethyl acetate (1:1) as eluent, to afford **14b** (0.36 mmol, 82%) as a yellow oil. $[\alpha]_D^{20}$: +37.0 (c 0.97, $CHCl_3$). ^{1}HNMR ($CDCl_3$): δ 1.52 (s, 3H), 1.55 (s, 3H), 1.74 (s, 3H), 3.94 (dd, 1H, J_1 8.2 Hz, J_2 7.4 Hz), 4.90 (d, 1H, *J* 8.4 Hz), 5.37 (dd, 1H, J_1 2.6 Hz, J_2 1.8 Hz), 5.44 (dd, 1H, J_1 7.4 Hz, J_2 2.6 Hz), 6.15 (dd, 1H, J_1 5.8 Hz, J_2 1.8 Hz), 7.31-7.34 (m, 5H), 7.50 (d, 1H, *J* 5.8 Hz) ppm. ^{13}CNMR ($CDCl_3$): δ 20.6 (q), 27.0 (q), 27.3 (q), 71.3 (d), 80.8 (d), 81.5 (d), 82.03 (d), 110.6 (s), 123.2 (d), 127.4 (2C, d), 128.9 (2C, d), 129.0 (d), 136.7 (s), 152.4 (d), 169.6 (s), 172.4 (s) ppm. IR: νmax 2985, 2929, 1755, 1222 cm^{-1}. HRMS-EI (M++Na): Calculated for $C_{18}H_{20}O_6Na$: 355.1152, experimental: 355.1134.

(*E*)-5-(((4R,5R)-2,2-Dimethyl-5-phenyl-1,3-dioxolan-4-yl)methylene)furan-2(5H)-one (15a). Diazobicycloundecane (0.6 mL, 4.25 mmol) was added to a solution of **14a** (280 mg, 0.85 mmol) in 5 mL of toluene under an argon atmosphere at room temperature. After 5h, water (5mL) was added and the reaction mixture was extracted with ethyl acetate. The combined organic phases were washed with brine and dried over Na_2SO_4. Evaporation of the solvent at reduced pressure afforded a crude product, which was fractionated by flash chromatography on silica gel. Elution with ethyl acetate: hexane = 7:3 afforded **15a** (148 mg, 65%) ^{1}HNMR ($CDCl_3$): δ 1.57 (s, 3H), 1.62 (s, 3H), 4.46 (dd, 1H, J_1 8.4 Hz, J_2 8.0 Hz), 4.72 (d, 1H, *J* 8.0 Hz), 5.73 (dd, 1H, J_1 8.0 Hz, J_2 1.4 Hz), 6.11 (dd, 1H, J_1 5.6 Hz, J_2 1.4 Hz), 7.27 (d, 1H, *J* 5.6 Hz), 7.34 (m, 5H) ppm. ^{13}CNMR ($CDCl_3$): δ 26.9 (q, 2C), 79.7 (d), 83.3 (d), 109.7 (d), 110.2 (s), 121.3 (d), 126.3 (2C, d), 128.7 (2C, d), 128.7 (d), 135.8 (s), 140.3 (d), 151.8 (s), 168.8 (s) ppm. Analc. Calc. for $C_{16}H_{16}O_4$: C, 70.57; H, 5.92; O, 23.50. Found: C, 70.60; H, 5.87; O, 23.22.

(*E*)-5-[(2*R*,3*R*)-2,3-Dihydroxy-3-phenylpropylidene]furan-2(5*H*)-one (*E*)-6. A catalytic amount of *p*-toluensulfonic acid was added to a solution of **15a** (50 mg, 0.18 mmol) in 5 mL methanol. The reaction was stirred for 12 hours at room temperature. Then, the organic solvent was evaporated off under reduced pressure, 5 mL of water was added and the mixture was extracted with chloroform. The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography, using hexane/ethyl acetate (3:7) as eluent, to afford (*E*)-**6** (0.13 mmol, 73%) as a yellow oil. $[\alpha]_D^{20}$: +95.5 (c 1.05, $CHCl_3$). ^{1}HNMR ($CDCl_3$): δ 3.11 (s, 1H), 3.36 (s, 1H), 4.48 (dd, 1H, J_1 7.6 Hz, J_2

7.4 Hz), 4.55 (d, 1H, *J* 7.6 Hz), 5.55 (ddd, 1H, J_1 7.4 Hz, J_2 1.7 Hz, J_3 0.5 Hz), 6.05 (dd, 1H, J_1 5.6 Hz, J_2 1.7 Hz), 7.27-7.34 (m, 5H), 7.47 (dd, 1H, J_1 5.6 Hz, J_2 0.5 Hz) ppm. ^{13}CNMR ($CDCl_3$): δ 73.1 (d), 77.7 (d), 112.7 (d), 120.9 (d), 126.7 (2C, d), 128.6 (d), 128.6 (2C, d), 139.1 (s), 140.9 (d), 151.4 (s), 169.2 (s) ppm. IR: νmax 3403, 1776, 1747, 1060 cm^{-1}. HRMS-EI (M++Na): Calculated for $C_{13}H_{12}O_4Na$: 255.0627, experimental: 255.0628.

(5*R*,7*R*,8*S*,9*S*)-9-Bromo-8-hydroxy-7-phenyl-1,6-dioxaspiro[4.4]non-3-en-2-one (7a) and **(5*R*,7*R*,8*S*,9*R*)-9-bromo-8-hydroxy-7-phenyl-1,6-dioxaspiro[4.4]non-3-en-2-one (7b).** A solution of **(E)-6** (122.4 mg, 0.52 mmol) in 5 mL of $CHCl_3$ was placed in a 50 mL round-bottommed flask. The solution was cooled to 0 ºC, after which NBS (140 mg, 0.8 mmol) and $NaHCO_3$ (65.6 mg, 0.8 mmol) were added. After 48 hours the reaction was completed and 5 mL of $CHCl_3$ was added. The organic solution washed successively with an aqueous 10% $Na_2S_2O_3$ solution, followed by brine and dried over anhydrous Na_2SO_4. Evaporation of the solvent under reduced pressure afforded a residue (200 mg), which was fractionated by flash chromatography with hexane/ethyl acetate (1:1) as eluent mixture, to afford 105.2 mg (65%) of mixture of **7a** and **7b** (3: 1).

7a. Colorless oil, ^{1}HNMR ($CDCl_3$): δ 4.62 (m, 1H), 4.82 (d, 1H, *J* 4.0 Hz), 5.51 (d, 1H, *J* 4 Hz), 6.20 (dd, 1H, J_1 5.5 Hz, J_2 1.0 Hz), 7.37-7.42 (m, 5H), 7.44 (dd, 1H, J_1 5.5 Hz, J_2 1.0 Hz) ppm. ^{13}CNMR ($CDCl_3$): δ 54.9 (d), 73.5 (d), 83.5 (d), 113.4 (s), 123.4 (d), 126.8 (2C, d), 128.5 (2C, d), 128.8 (d), 133.9 (s), 152.4 (d), 169.2 (s) ppm. HRMS-EI (M++Na): Calculated for $C_{13}H_{11}O_4BrNa$: 332.973291, experimental: 332.9742.

7b. Colorless oil, ^{1}HNMR ($CDCl_3$): δ 4.48 (s, 1H), 4.61 (m, 1H), 5.91 (d, 1H, *J* 4.3 Hz), 6.31 (dd, 1H, J_1 5.7 Hz, J_2 1.0 Hz), 7.37-7.42 (m, 5H), 7.5 (d, 1H, *J* 5.7 Hz) ppm. ^{13}CNMR ($CDCl_3$): δ 54.8 (d), 79.4 (d), 86.5 (d), 114.3 (s), 125.4 (d), 126.5 (2C, d), 128.6 (2C, d), 128.7 (d), 134.0 (s), 151.6 (d), 170.7 (s) ppm. HRMS-EI (M++Na): Calculated for $C_{13}H_{11}O_4BrNa$: 332.9733, experimental: 332.9742.

(+)-8-*epi*-Crassalactone D and 5,8-*epi*-crassalactone D (1b and 1c). A solution of a mixture of bromolactones **7a** and **7b.** (3 : 1) (62.8 mg, 0.2 mmol) in toluene (6 mL) was placed in a 50 mL round-bottomed-flask. The solution was kept in an inert atmosphere and warmed to reflux temperature. At this temperature a catalytic amount of AIBN was added and shortly after Bu_3SnH (64 μL, 0.24 mmol) was added dropwise. The reaction mixture was stirred at the same temperature for 25 min, after which it was cooled to room temperature. Then, the mixture was poured over a saturated aqueous solution of NaF. The solution was stirred for 4 h, extracted with ethyl acetate, washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash chromatography, using hexane/ethyl acetate (1:1) as eluent, to afford **1b** (35 mg, 75%) and **1c** (11.5 mg, 25%).

1b. Colorless oil, $[\alpha]_D^{20}$: -20.6 (c 0.82, $CHCl_3$). ^{1}HNMR ($CDCl_3$): δ 2.53 (dd, 1H, J_1 14.7 Hz, J_2 1.1 Hz), 2.81 (dd, 1H, J_1 14.7 Hz, J_2 5.3 Hz), 4.62-4.65 (m, 1H), 5.43 (d, 1H, *J* 3.1 Hz), 6.16 (dd, 1H, J_1 5.5 Hz, J_2 1.1 Hz), 7.36-7.38 (m, 5H), 7.38 (d, 1H, *J* 5.5 Hz) ppm. ^{13}CNMR ($CDCl_3$): δ 43.1 (t), 73.7 (d), 86.6 (d), 113.6 (s), 122.7 (d), 126.6 (2C, d), 128.6 (d), 128.7 (2C, d), 134.1 (s),

152.9 (d), 169.9 (s) ppm. IR: νmax 3463, 3052, 2984, 1768, 1264, 1168, 1028 cm^{-1}. HRMS-EI (M++Na): Calculated for $C_{13}H_{12}O_4Na$: 255.0628, experimental: 255.0621.

1c. Colorless oil, $[\alpha]_D^{20}$: -16.8 (c 0.56, $CHCl_3$). ^{1}HNMR ($CDCl_3$): δ 2.54 (d, 1H, *J* 14.0 Hz), 2.63 (dd, 1H, J_1 14.0 Hz, J_2 4.8 Hz), 4.59-4.61 (m, 1H), 5.40 (d, 1H, *J* 4.1 Hz), 6.25 (d, 1H, J_1 5.6 Hz), 7.21 (d, 1H, *J* 5.6 Hz), 7.40-7.43 (m, 5H) ppm. ^{13}CNMR ($CDCl_3$): δ 40.3 (t), 72.8 (d), 88.9 (d), 114.0 (s), 124.4 (d), 126.6 (2C, d), 128.3 (d), 128.5 (2C, d), 135.1 (s), 151.6 (d), 169.1 (s) ppm. IR: νmax 3463, 3054, 2986, 1776, 1422, 1265 cm^{-1}. HRMS-EI (M++Na): Calculated for $C_{13}H_{12}O_4Na$: 255.0628, experimental: 255.0614.

(+)-Crassalactone D benzoate (18). Triphenylphosphine (34.6 mg, 0.13 mmol) and benzoic acid (16.1 mg, 0.13 mmol) were added to a solution of **1b** (25 mg, 0.11 mmol) in 2 mL of freshly distilled THF. The solution was kept at room temperature in an inert atmosphere and then diethyl azodicarboxylate (DEAD) (40% in THF) (60 μL, 0.13 mmol) was added dropwise. The reaction mixture was stirred for 24 hours at the same temperature and then concentrated under reduced pressure. The residue was fractionated by flash chromatography, using hexane/ethyl acetate (6:4) as eluent mixture, to afford **18** (28.6 mg, 75%).

$[\alpha]_D^{20}$: +22.8 (c 0.25, $CHCl_3$). ^{1}HNMR ($CDCl_3$): δ 2.51 (dd, 1H, J_1 14.8 Hz, J_2 1.5 Hz), 2.75 (dd, 1H, J_1 14.8 Hz, J_2 6.8 Hz), 5.56 (ddd, 1H, J_1 6.8 Hz, J_2 2.7 Hz, J_3 1.5 Hz), 5.64 (d, 1H, *J* 2.7 Hz), 6.31 (d, 1H, *J* 5.6 Hz), 7.32 (d, 1H, *J* 5.6 Hz), 7.42-7.51 (m, 10H) ppm. ^{13}CNMR ($CDCl_3$): δ 40.2 (t), 79.3 (d), 88.1 (d), 113.7 (d), 125.0 (d), 125.3 (d), 128.4 (2C, d), 128.5 (2C, d), 128.7 (2C, d), 129.3 (s), 129.9 (2C, d), 130.1 (d), 137.8 (s), 151.0 (d), 166.2 (s), 169.6 (s) ppm. HRMS-EI (M++Na): Calculated for $C_{20}H_{16}O_5Na$: 359.0890, experimental: 359.0891.

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