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Chemical Transformation of Prostaglandin-A_2: A Novel Series of C-10 Halogenated, C-12 Hydroxylated Prostaglandin-A_2 Analogues

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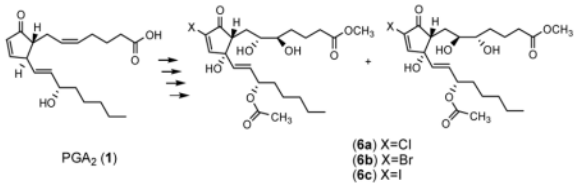
Abstract



Synthesis of a novel class of C-10 halogenated and C-12 oxygenated prostaglandin-A_2 derivatives 6(a–c) has been accomplished. (15*S*)-Prostaglandin-A_2 (1), from the gorgonian *Plexaura homomalla*, served as the starting material for the synthesis. The absolute configuration was determined using NMR.

Δ^{12}-Prostaglandin J2 (Δ^{12}-PGJ_2), a cross-conjugated enone, is known to inhibit ubiquitin specific isopeptidase activity causing apoptosis.[1] Mechanistic studies have indicated that inhibition results from Michael addition of an isopeptidase cysteine residue to the endocyclic β-carbon of the cyclopentenone.[2] Punaglandins (PNGs), C-10 chlorinated and C-12 oxygenated prostanoids, are more potent inhibitors of isopeptidase activity than Δ^{12}-PGJ_2 and the PGA series (Figure 1).[3] On the basis of these results, increasing the electrophilicity of the endocyclic β-carbon (C-10) should increase reactivity. To test this hypothesis, a new series of halogenated PGA_2 derivatives were synthesized (**4a–4c**) by substituting electron withdrawing groups (Cl, Br, I) at the α-position of PGA_2 (Scheme 1).

Preliminary work with these α-halogenated PGA_2 analogues (**4a–4c**) indicated that the potency of isopeptidase inhibition for the series is I≫Br≥Cl.[4] Additionally, Iodo-PGA_2 was a more potent inhibitor of ubiquitin specific isopeptidase activity compared to Δ^{12}- PGJ_2, but less potent than the PNGs. Thus it was recognized that halogenation and electophilicity do play a role in the ability of prostaglandins to inhibit ubiquitin isopeptidase activity, but are not the only factors. These results suggested C-12 hydroxylation similar to PNGs may be necessary to achieve optimum activity. To test this hypothesis, a series of C-10 halogenated and C-12 oxygenated PGA_2 derivatives (**6a–6c**) have been synthesized (Scheme 3).[4]

The starting material for the synthesis, (15*S*)-prostaglandin-A_2 (PGA_2) was isolated in abundance (5.7% recovery)[5] from the gorgonian *Plexaura homomalla*.[6] The side-chain functional groups of PGA_2 (the terminal carboxylic acid at C-1 and the alcohol at C-15) were

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blocked as their methyl ester and acetate respectively, using standard derivatization conditions (Scheme 1).[7]

The 15-*O*-acetyl-PGA_2 methyl ester (**2**) was treated with alkaline hydrogen peroxide at −15 °C to generate a mixture of C(10,11)- α,β-epoxides (**3**).[8] The subsequent C-10 halide substitutions[9] were achieved by regioselective ring opening of the C(10,11)-epoxide (**3**) with halide (Cl, Br, I) salts under mildly acidic conditions (Amberlyst 15[10] or silica gel support[11]). Similar transformations of epoxy cyclopentenones into α-haloenones have been shown to occur via the halohydrin intermediates which are spontaneously dehydrated under acidic conditions to afford the vinylhalide products.[10]

Accordingly, the method of choice for the formation of vinylchloride (**4a**) was LiCl/Amberlyst/CH_3CN system, where as the vinylbromide (**4b**) was formed by NaBr under otherwise identical conditions.[12] However, attempts to form the vinyl iodide (**4c**) under similar conditions (LiI or NaI/Amberlyst/CH_3CN) were unsatisfactory and resulted in the re-formation of the alkene (**2**). A subsequent literature survey of alternative methods of vinyliodide formation[13] from epoxides, revealed that silica gel could be employed as an efficient acid catalyst in the nucleophilic ring-opening of epoxides under solvent-free conditions.[11] Accordingly, the solvent-free iodination of epoxide (**3**) was carried out using LiI supported on silica gel. The reaction proceeded smoothly to give 54% of the vinyliodide (**4c**) along with 13% of the alkene by-product (**2**).

The next task of the synthesis was the conversion of the C-10 halogenated PGA_2 series (**4a–4c**) to the corresponding C-12 hydroxylated derivatives (**6a–6c**). This novel series of C-12 hydroxylated derivatives were believed to be accessible via allylic oxidation mediated by selenium dioxide,[14] owing to the fact that the C-12 position of PGA_2 is bis-allylic to C-10 and C-13 double bonds (Scheme 2). However, the likely formation of byproducts due to multiple potential oxidation sites, were foreseen as a possible drawback of this method.

To test the feasibility of the allylic oxidation reaction, PGA_2-acetate methyl ester (**2**) was employed. As speculated, compound **2** with SeO_2 gave several oxidation by-products. One major by-product was identified as the conjugated diene (**2a**) possibly arising from allylic hydroxylation at C-7 followed by dehydration (Scheme 2). Shorter reaction times, lower reflux temperatures (95% EtOH) or reduced amounts of the oxidant did not facilitate formation of the desired tertiary alcohol product (**6**).

It was now evident that in order to selectively hydroxylate the bis-allylic position (C-12) of PGA_2 and suppress by-product formation during SeO_2 oxidation, the other allylic positions (C-4 and C-7) needed to be removed or masked in some manner. This was achieved by selective epoxidation of the C(5,6) double bond in **4** using *m*-CPBA (Scheme 3). The resulting C(5,6)-α,β-epoxide mixture (**5**) was treated as an intermediate and used without further purification for the SeO_2 oxidation. As anticipated, allylic hydroxylation at C-12 position proceeded smoothly and was accompanied by C(5,6)-epoxide ring opening to yield the novel series of prostaglandin-A_2 analogues (**6a–6c**)[15] in moderate yields (Scheme 3).

The relative and absolute configurations of the five stereocenters (C-5/6/8/12/15) in **6(a–d)** were deduced as follows. The absolute stereochemistry of C-8 was assumed (*R*), based on literature precedent for coral-derived PGA_2.[16] The assignment of the 15(*S*) configuration of **6** was based on the application of Mosher's method[17] to (*S*)- and (*R*)-MPA derivatives of PGA_2-methyl ester.[18] The *trans* (*R*,*R*) relationship between the two side chains (C-8/C-12) was established based on a strong NOESY cross peak observed between H-8 and H-13. Subsequent molecular modeling studies with energy-minimized conformations for each of the C-12 epimers supported this observation. The *trans*-(8*R*,12*R*) relationship was further

corroborated by heteronuclear coupling constant analysis ($^2J_{H8/C12}$ = small)[19], and dihedral angle measurements (−135.7°) for the 8(*R*),12(*R*) diastereomer of **6**.[20]

The *cis* orientation of the C(5,6) epoxide mixture [(5S,6R) and (5R,6S) diastereomers] in **5** was supported by the homonuclear coupling constant value of $^3J_{H5/H6}$ = 4.3 Hz.[21] It was presumed that the C(5,6) diol in **6**, generated during the allylic oxidation (SeO_2/dioxane/H_2O/ reflux) of **5**, occurs via nucleophilic opening of the C(5,6) epoxide by water. Accordingly, non-regioselective attack of water on the (5*S*,6*R*) and (5*R*,6*S*) *cis*-epoxides in **5** would generate two secondary alcohol diastereomers, (5*R*,6*R*) and (5*S*,6*S*). This was supported by the ^{1}H-NMR spectra of **6(a–d)** which showed doubling of resonances due to the formation of two diastereomers in a ~1:1 ratio. Accordingly, HPLC analysis of **6d** showed two peaks eluting at 11.5 (**7**) and 13 min (**8**). The two peaks (**7** and **8**) were separated,[22] and were employed for absolute stereochemical assignments of the C(5,6) centers by *J*-based analysis,[19] Mosher's method[17] in conjunction with molecular modeling studies (Figure 2).

Initial attempts focused on utilizing *J*-based analysis[19] to relate the configuration of the vicinal diol segment C(5,6) to that of the known absolute configuration at C-8. However, diastereomer **7** proved undesirable for *J*-analysis due to overlap of resonances for H-5 and H-6 (δ3.51–3.57, m, 2H) as well as for H-7_h and H-7_l (δ 1.98, m, 2H). Therefore, the viable alternative was to attempt the *J*-based analysis on the diastereomer **8**.

For diastereomer **8**, sufficient chemical shift dispersion of all proton resonances were observed in $CDCl_3$ at 0 °C. While all of the couplings required for *J*-analysis were determined successfully (Table 1), the information failed to fit any of the typical rotamers with certainty.[19]

The reason for the occurrence of atypical coupling values in **8** could be explained based on a molecular modeling study, which revealed that the cyclopentenone carbonyl (C-9) is involved in an intra-molecular H-bonding with C-6(OH) adopting a seven-membered cyclic conformation (Figure 3). The measured *J*-values and NOESY data were in accordance with such a seven-membered conformation.

Having failed to unequivocally determine the C(5,6) stereochemistry by *J*-based analysis, Mosher's method was attempted on **8**. Accordingly, reaction of **8** with (*R*)- and (*S*)-MPA acids[23] was expected to yield the corresponding C(5,6)-*bis*-MPA esters. However, ^{1}H-NMR data confirmed that the C-5 MPA derivative was the sole product. Comparison of the chemical shift differences ($\Delta\delta = \delta_R - \delta_S$) in the ^{1}H-NMR spectra of the C-5 (*R*)- and (*S*)-MPA derivatives of **8** at 0 °C indicated the absolute configuration was (*R*) (Figure 4).

Thus the absolute configuration of all five stereo-centers (C-5/6/8/12/15) in **8** was established as (5*R*,6*R*,8*R*,12*R*) and 15(*S*). Consequently, the absolute configuration of the diol diastereomer **7** was assigned as (5*S*,6*S*,8*R*,12*R*) and 15(*S*). The absolute configuration assignments of **7** and **8** were in good agreement with their ^{1}H NMR data, coupling constant analysis and molecular modeling studies employing MM2 and AM1.[24]

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

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15. NMR data were recorded at 0 °C. Compounds stored at r.t. tend to decompose slowly over 3–5 days.
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21. Due to the overlap of H-5 and H-6, a combination of ^{1}H-NMR, HOMODEC and 1D-TOCSY experiments were employed to extract the coupling constants with certainty.
22. See Experimental section for details of the separation procedure.
23. 2 eqvi. of MPA per OH was employed. Reaction was carried out at room temperature for ~16 h, until complete convertion to the product, as indicated by TLC and NMR.
24. CS Chem3D Pro; ChembridgeSoft Corporation: Cambridge, MA.

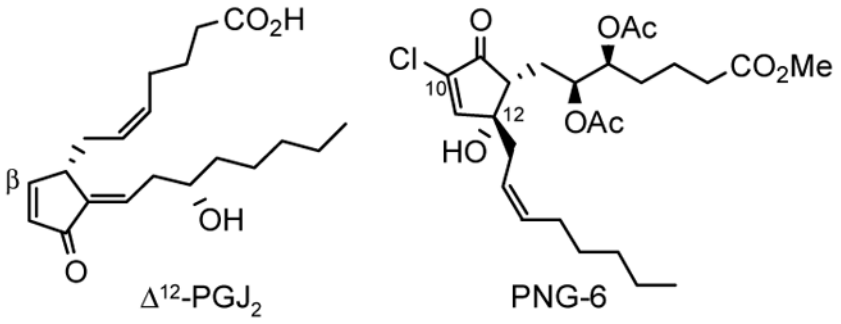
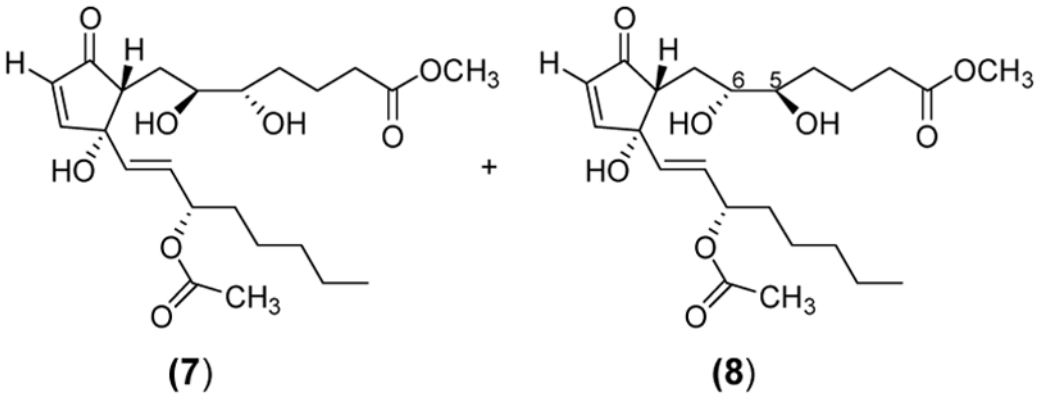


Figure 1.
Electrophilic prostanoids



(7) (8)

Figure 2.
C(5,6)-diol diastereomers of **6d**

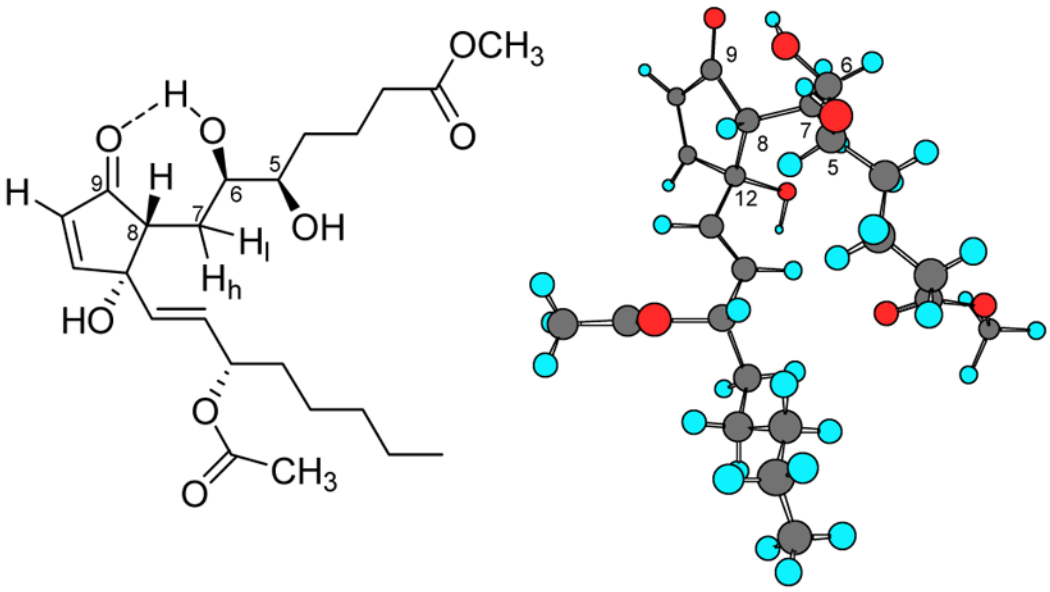


Figure 3.
The MM2/AM1-optimized model for **8**

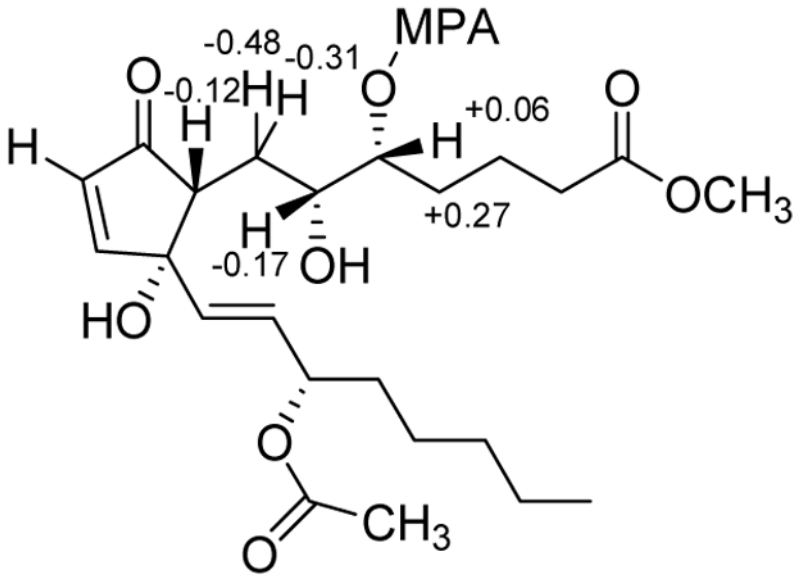
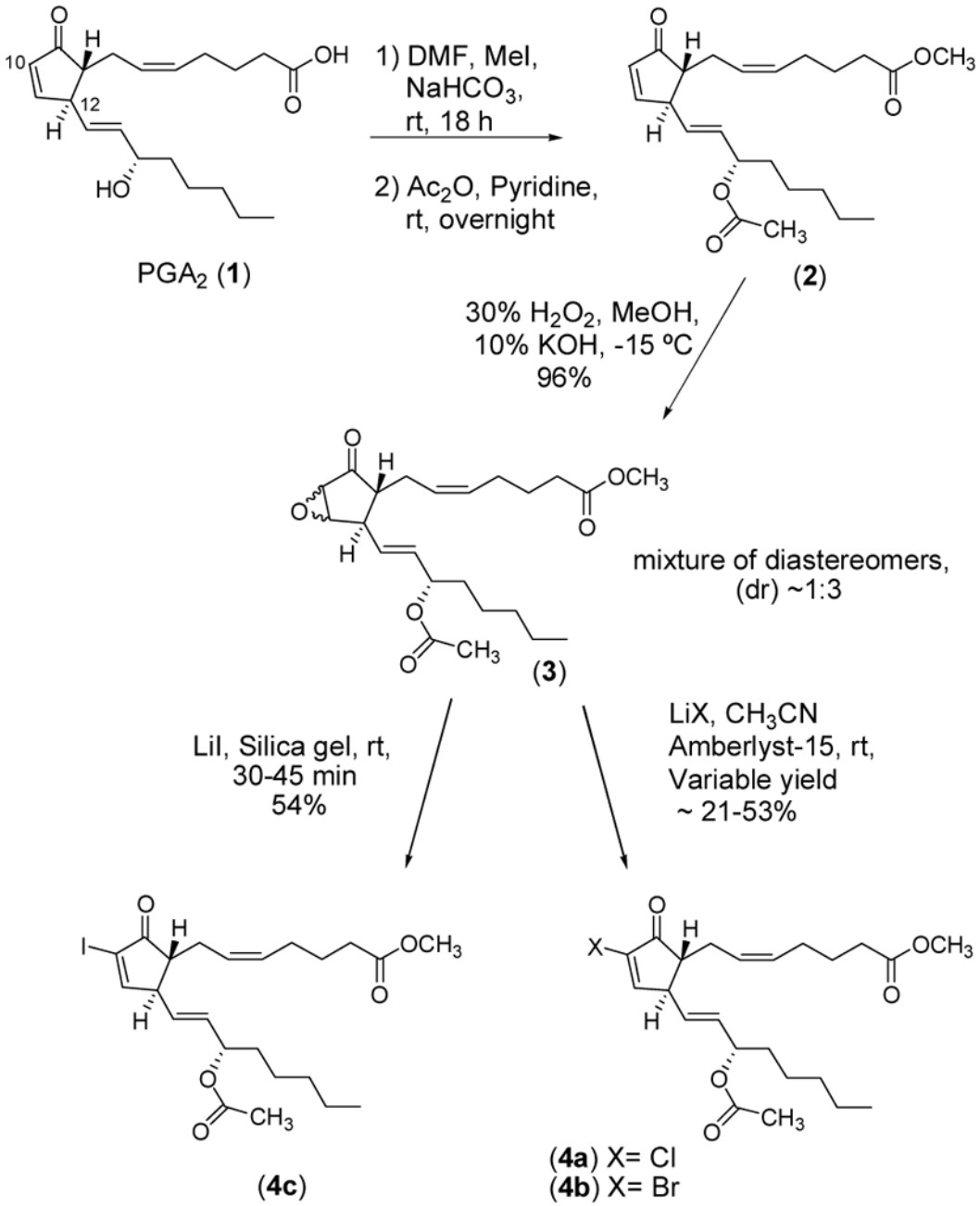
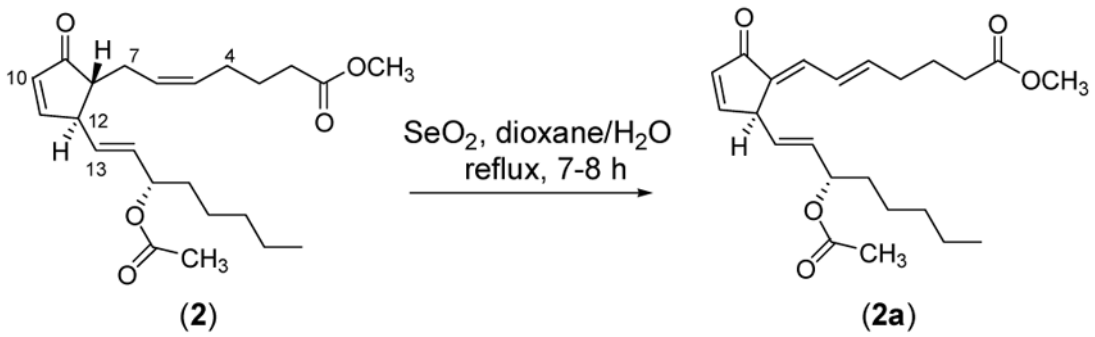


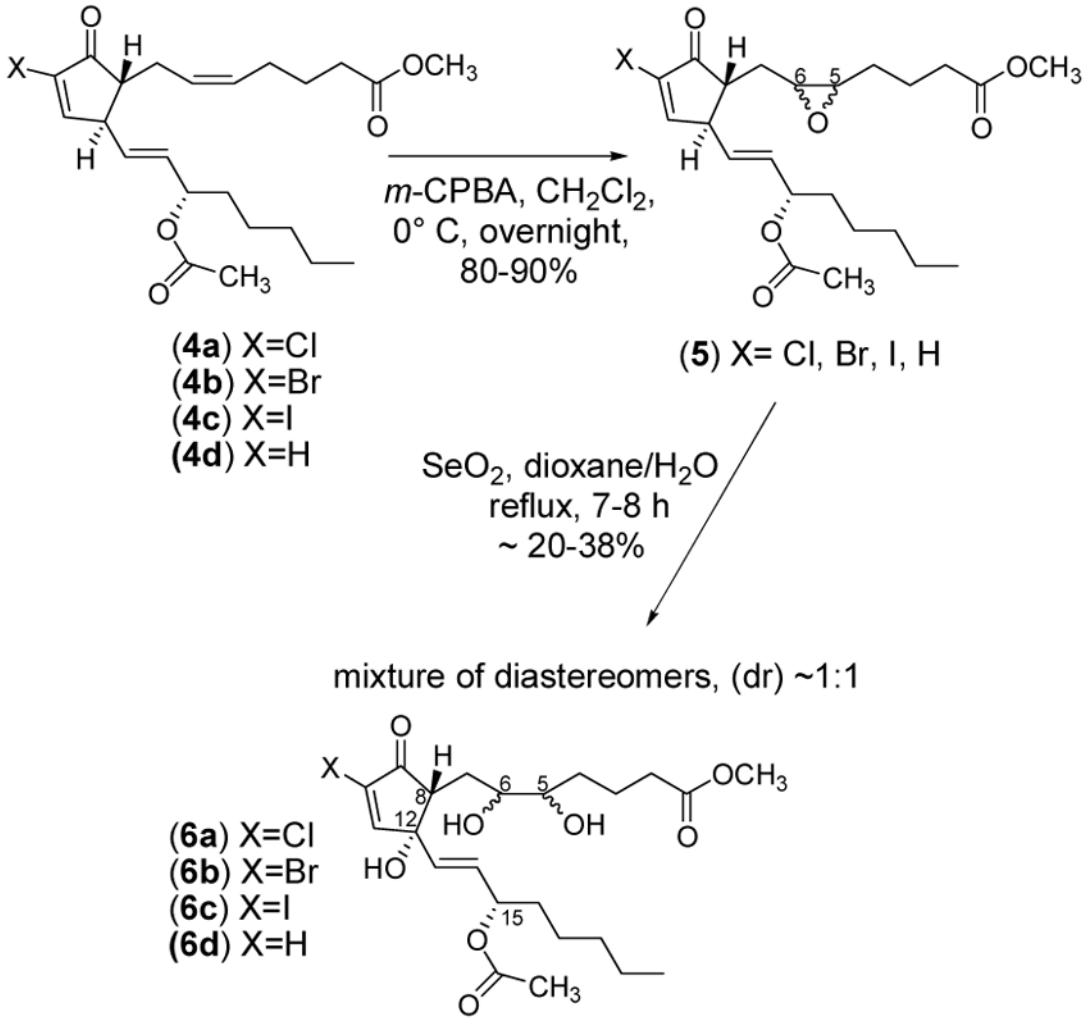
Figure 4.
Δδ values for 8 (Δδ = $\delta_R - \delta_S$, 500 MHz, $CDCl_3$, 0 °C)



Scheme 1.
Synthesis of α-halogenated PGA_2 analogues



Scheme 2.
SeO_2 oxidation of **2**



Scheme 3.
Synthesis of C-12 oxygenated PGA_2 derivatives

Table 1

$^{2,3}J$ values of **8** for the C-6/C-7 segment measured in $CDCl_3$

$^{2,3}J$ values[a]	J (Hz)	classification[b]
^{3}J (H-6, H-7_h)	+ 6.3	medium
^{3}J (H-6, H-7_l)	+ 6.3	medium
^{3}J (H-6, C-8)	+ 2.2	small
^{3}J (H-5, H-7_h)	+4.4	medium
^{3}J (H-5, H-7_l)	+2.2	small
^{2}J (C-6, H-7_h)	−4.3	medium
^{2}J (C-6, H-7_l)	−1.1	small

[a] $H\text{-}7_h$ and $H\text{-}7_l$ represent the high- and low-field H-7 protons respectively.

[b] Classification for magnetude of the coupling constants: values between large and small are regarded as medium[19]