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Ring opening metathesis approach to the isoprostanes†

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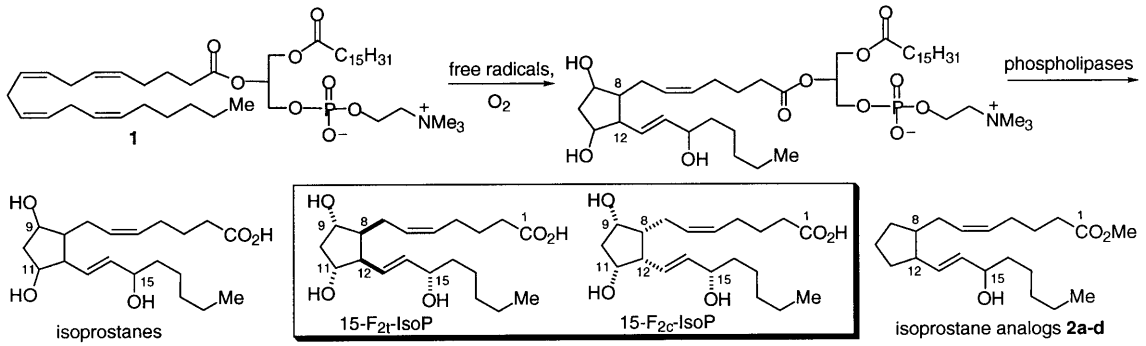
Abstract

A new route to enantiomerically pure isoprostane analogs is described. Ring opening metathesis of bicyclo[3.2.0]heptene (**3**) with TBS-protected allyl alcohol generates the *syn*-disubstituted cyclopentyl product (±)-**4**. Diene (±)-**4** can be converted in a straightforward manner to aldehyde (±)-**7**. Asymmetric alkylations of aldehyde (±)-**7** yield a series of enantiomerically pure isoprostane analogs (**2a**–**d**).

The isoprostanes, a recently discovered class of human serum metabolites, are the result of in vivo peroxidation of membrane-bound arachidonic acid (**1**) (Scheme 1).[1] Unlike the prostaglandins, the isoprostanes are believed to arise predominately from a cyclooxygenase-independent free radical-initiated oxidation of **1**.[2] The non-enzymatic generation of these endogenous molecules is presumed to occur without substantial stereochemical control. Subsequent release of the membrane-bound isoprostanes by phospholipases produces the free acids, which



Scheme 1.

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† Dedicated to our friend Harry S. Wasserman on the occasion of his 80th birthday.

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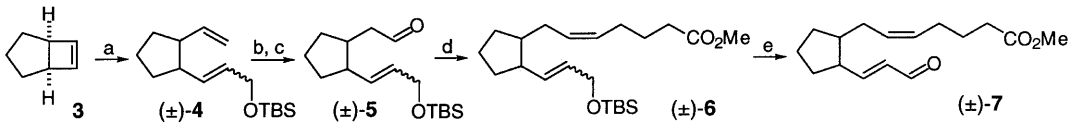
have been detected in human plasma and urine samples.[3] Accordingly, racemic isoprostanes have been recognized as valuable markers of oxidative stress.[4]

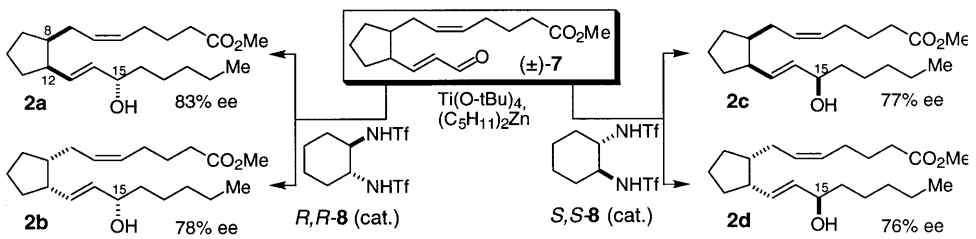
Given the role of lipid oxidation in the progression of diseases such as diabetes and atherosclerosis, the metabolic functions of the isoprostanes are of great interest.[5] The isoprostanes have been reported to be potent vasoconstrictors, smooth muscle growth factors,[6] and platelet aggregation factors,[7] as well as to possess other biological activities.[8] The specific cellular targets for these molecules, however, are unknown. To better understand the cellular interactions and activities of the isoprostanes, we are seeking to access useful structural variants through total synthesis.[9] The synthetic strategy described herein provides individual enantiomers of a diastereomeric pair of isoprostane analogs that differ in the absolute and relative stereochemistry of C8 and C12 versus C15 (**2a**–**d**, Schemes 1 and 3).

The preparation of the isoprostane analogs starts with cyclobutene **3**, a known compound readily available in multi-gram quantities through a photocyclization of 1,3-cycloheptadiene.[10] As illustrated in Scheme 2, ring opening metathesis of cyclobutene **3** with TBS-protected allyl alcohol produces diene **4** in 56% yield as a mixture of olefin stereoisomers (*Z*:*E* 2.3:1).[11] The olefin isomers could be separated by silica gel chromatography or more easily carried through as a mixture, where they converge to a single compound at a later point in the synthesis (i.e. **6**→**7**). Selective hydroboration of diene **4** with disiamylborane, followed by oxidative work-up provided the corresponding alcohol in 88% yield. Oxidation of the alcohol to aldehyde **5** was accomplished with PCC and basic Al_2O_3 in CH_2Cl_2. Wittig olefination of aldehyde **5** with commercially available (4-carboxybutyl)triphenylphosphonium bromide (deprotonated with KHMDS in THF) afforded, after work-up with $TMSCHN_2$, methyl ester **6** in 87% yield. Removal of the TBS protecting group under oxidative conditions was achieved using PCC in CH_2Cl_2 at room temperature for 48 h. The resultant aldehyde (±)-**7** was isolated as a single olefin isomer in 75% yield.



Scheme 2. (a) $(Cy_3P)_2Cl_2Ru{=}CHPh$, $H_2C{=}CHCH_2OTBS$, CH_2Cl_2, 23°C (56%); (b) Sia_2BH, THF, 0°C; H_2O_2, NaOH, H_2O (88%); (c) PCC, Al_2O_3, CH_2Cl_2 (95%); (d) $(Ph_3P(CH_2)_4CO_2H)^+Br^-$, KHMDS, THF, 23°C; $TMSCHN_2$ (87%); (e) PCC, CH_2Cl_2, 23°C, 48 h (75%)

As a means to access each isoprostane stereoisomer independently, a reagent-controlled enantioselective addition of dipentylzinc to racemic aldehyde (±)-**7** was enlisted (Scheme 3). Several conditions for the alkylation were explored (Table 1). Initial experiments using Ti(*i*-



Scheme 3.

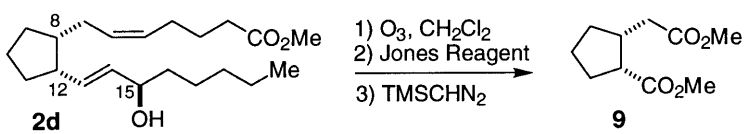
Table 1

Entry	Ti (equiv.)	$Zn(C_5H_{11})_2$	Ligand (mol%)	Temp (°C)	Time (h)	Yield (%)	Products (% ee)[a]	
(1)	Ti(*i*-PrO)$_4$ (2.0)	3.0 equiv.	*R*,*R*-**8** (6)	−20	5	62	**2a** (0)	**2b** (0)
(2)	Ti(*t*-BuO)$_4$ (2.3)	2.5 equiv.	*R*,*R*-**8** (11)	25	6	65	**2a** (68)	**2b** (76)
(3)	Ti(*t*-BuO)$_4$ (2.3)	2.5 equiv.	*R*,*R*-**8** (10)	4	30	80	**2a** (83)	**2b** (78)
(4)	Ti(*t*-BuO)$_4$ (2.3)	2.6 equiv.	*R*,*R*-**8** (20)	25	2	59	**2a** (73)	**2b** (80)
(5)	Ti(*t*-BuO)$_4$ (2.1)	2.5 equiv.	*R*,*R*-**8** (10)	45	2.5	45	**2a** (31)	**2b** (22)
(6)	Ti(*t*-BuO)$_4$ (2.1)	2.5 equiv.	*R*,*R*-**8** (10)	−20	20	79	**2a** (34)	**2b** (39)
(7)	Ti(*t*-BuO)$_4$ (1.5)	2.0 equiv.	*R*,*R*-**8** (10)	4	13	80	**2a** (70)	**2b** (75)
(8)	Ti(*t*-BuO)$_4$ (2.5)	2.7 equiv.	*S*,*S*-**8** (11)	4	16	92	**2c** (77)	**2b** (76)

[a] Enantiomeric excesses were determined by ^{19}F NMR analysis of the corresponding Mosher ester.

PrO)$_4$, $Zn(C_5H_{11})_2$, and ligand (*R*,*R*)-**8** (Table 1, entry 1) resulted in the formation of readily separable diastereomeric products (**2a**–**d**), each as a racemic mixture. Replacement of the Ti(*i*-PrO)$_4$ with Ti(*t*-BuO)$_4$ (entries 2–8), however, led to the formation of the diastereomeric products (1:1) with improved enantioselectivity.[12] Increasing the catalyst loading from 10 to 20 mol% (entry 4) did not improve the selectivity or yield of the reaction. Interestingly, a decrease in selectivity was observed by either raising or lowering the reaction temperature (entries 5 or 6 compared to entry 3). Adjustments to the reagent and catalyst ratios also had little influence on the selectivity of the reaction (entry 7). Entry 3 represents the optimal conditions identified for asymmetric alkylation of aldehyde (±)-**7**. Under these conditions, the isoprostane analogs **2a** and **2b** could be prepared in 83 and 78% ee, respectively. Simply switching to the (*S*,*S*)-**8** ligand generated the enantiomers of the diastereomeric pair (**2c** and **2d**) with comparable selectivity (entry 8).

The absolute stereochemistry at C15 was determined through NMR analysis of the Mosher ester.[13] The newly formed stereocenter at C15 was determined to be of the *S* configuration for compounds **2a** and **2b**. The absolute stereochemical configuration at C8 and C12 of **2a** and **2b** was determined by chemical correlation of **2a** with the known compound **9** (Eq. (1)).[14] Ozonolysis of **2d**, followed by oxidation with Jones reagent and work-up with $TMSCHN_2$ gave diester **9** ($[\alpha]_D^{23} = -10°$, *c* 0.0005, MeOH), a compound matching the optical rotation and ^1H NMR spectra reported for (−)-**9**.



(1)

In summary, the concise preparation of four stereochemically distinct isoprostane analogs has been described. A ring opening metathesis serves as a key transformation. A reagent-controlled enantioselective addition of dipentylzinc to racemic aldehyde (±)-**7** furnishes the enantiomerically enriched isomers **2a**–**d**. The modular nature of the synthesis allows for the selective preparation of numerous analogs. Since the in vivo, non-cyclooxygenase-mediated cyclization of arachidonic esters leads to isoprostane stereoisomers, the stereodivergent nature of the strategy has the advantage of selectively generating stereochemically distinct isoprostane reagents. Access to these potential probe reagents will lead to a better understanding of the cellular interactions responsible for the wide range of isoprostanes' biological activities. Efforts along these lines are underway.

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