Total Synthesis

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Total Synthesis of Δ^{12}-Prostaglandin J_3, a Highly Potent and Selective Antileukemic Agent**

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Dedicated to Professor E. J. Corey on the occasion of his 86th birthday

Abstract: *A catalytic asymmetric total synthesis of the potent and selective antileukemic Δ^{12}-prostaglandin J_3 (Δ^{12}-PGJ_3) is described. The convergent synthesis proceeded through intermediates **2** and **3**, formed enantioselectively from readily available starting materials and coupled through an aldol reaction followed by dehydration to afford stereoselectively the cyclopentenone alkylidene structural motif of the molecule.*

Recent reports described Δ^{12}-prostaglandin J_3 (Δ^{12}-PGJ_3, **1**, Figure 1) as a potent and selective ablator of leukemia stem cells in vitro and in vivo.[1,2] In view of the increasing interest in cancer stem cells as drivers for growth, perpetuation, recurrence, and drug resistance in various types of cancer,[3] Δ^{12}-PGJ_3 may serve as an important tool to decipher cancer biology and a lead compound for drug discovery and development. Naturally formed from ω-3 eicosapentaenoic acid ((5*Z*,8*Z*,11*Z*,14*Z*,17*Z*)-5,8,11,14,17-icosapentaenoic acid, EPA),[1,2,4] this secondary metabolite was isolated in minute amounts and characterized by UV spectroscopic and mass spectrometric methods.[1,2] The impressive in vitro potency and selectivity of Δ^{12}-PGJ_3 against chronic myelogenous leukemia (CML) stem cells ($IC_{50} = 12$ nM) and its ability to effectively cure this form of leukemia in a mouse model,[1,2] coupled with its scarcity, prompted us to undertake its total synthesis with the intention of rendering it readily available for thorough biological investigations and full structural characterization.

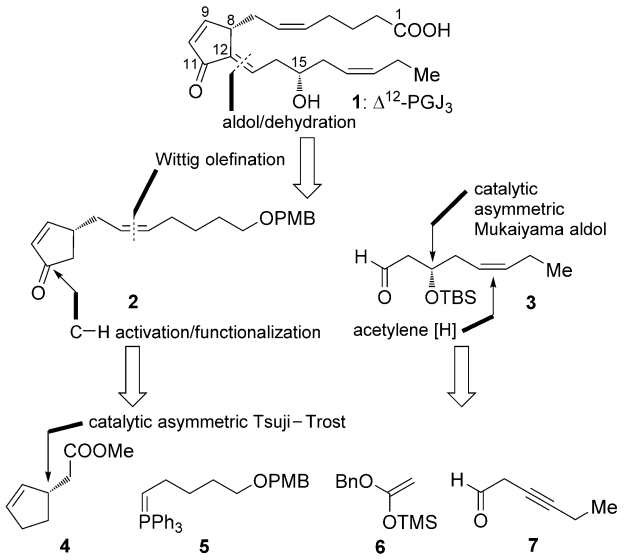

Figure 1. Retrosynthetic analysis of Δ^{12}-PGJ_3 (**1**).

The molecular structure of Δ^{12}-PGJ_3 (**1**) is characterized by its 2-alkylidene cyclopentenone structural motif, and while stable by itself it could, in principle, undergo conjugate nucleophilic attack by thiols, particularly at the endocyclic double bond[4,5] (i.e. C9, prostaglandin numbering). This property may or may not be involved in the mechanism of action of this intriguing molecule. The *E*-configuration of the Δ^{12}-olefinic bond was presumed on the basis of thermodynamic stability. Figure 1 summarizes, in retrosynthetic format, the devised strategy for a catalytic asymmetric total synthesis of Δ^{12}-PGJ_3 (**1**). Disconnection of the Δ^{12}-olefinic bond through an aldol/dehydration process led to advanced intermediates cyclopentenone **2** and aldehyde **3**. These intermediates were then traced back to building blocks **4** and **5** (for **2**) and **6** and **7** (for **3**) through a Wittig olefination and an asymmetric Mukaiyama aldol reaction, respectively. The latter was intended to secure the configuration of the asymmetric center at C15, while a palladium-catalyzed asymmetric Tsuji–Trost alkylation reaction was reserved to install, using as precursor cyclopentenol acetate **9** (Scheme 1), the other remote stereocenter (C8) in its proper configuration. The required oxygenation at C11 was to be achieved through a C–H activation/functionalization process at the

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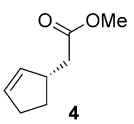
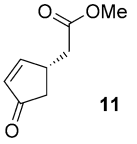
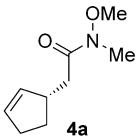
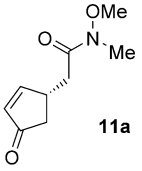
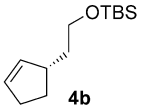
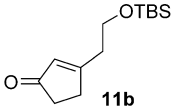
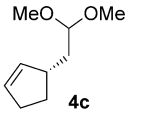
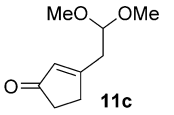
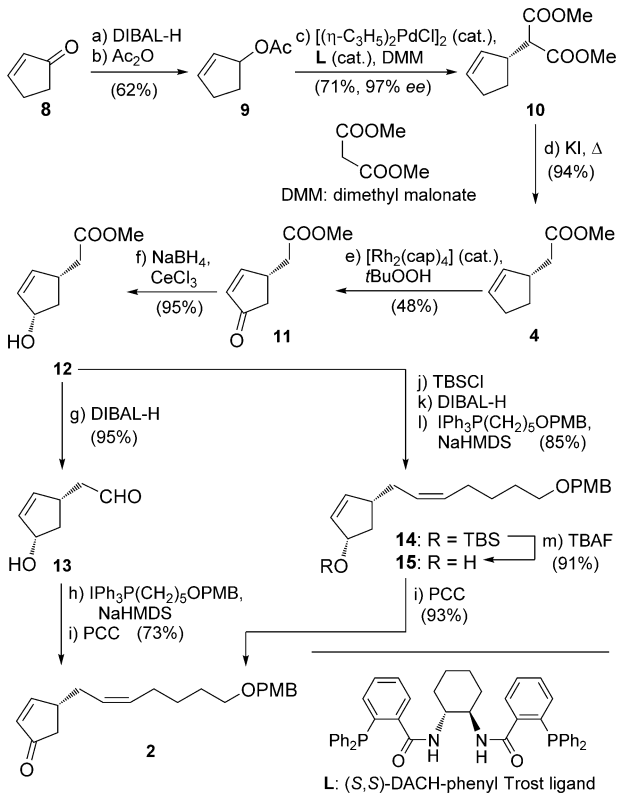
stage of building block **4**. While this strategy includes similar features to that employed by the Kobayashi group[6] to synthesize a related compound (Δ^{12}-PGJ$_2$),[6,7] it differs from it in significant ways, including the catalytic asymmetric Tsuji–Trost reaction to install the stereocenter at C8, the C–H activation/oxygenation of C11, and the application of the catalytic asymmetric Mukaiyama aldol reaction to install the stereocenter at C15.

Scheme 1 summarizes the formation of advanced intermediate **2** starting from commercially available 2-cyclopentenone (**8**) via intermediates **9** and **10**. By modifying reported procedures,[8] **8** was first converted to cyclopentenol acetate **9** (DIBAL-H reduction followed by acetylation, 62% overall yield; similar results were obtained with $LiAlH_4$ or $NaBH_4$/$CeCl_3$ as reducing agents, see the Supporting Information), and thence to dimethyl ester **10** through a palladium-catalyzed Tsuji–Trost asymmetric coupling reaction[9] with dimethyl malonate (DMM) in the presence of catalytic amounts of $[\eta^3\text{-}C_3H_5PdCl]_2$ and (*S*,*S*)-DACH-phenyl Trost ligand and Cs_2CO_3 (71% yield, 97% *ee*[10]). Monodecarboxylation of **10** (KI, 130 °C) then furnished intermediate **4** in 94% yield. The desired C–H activation/functionalization of **4** to its enone counterpart **11** required considerable experimentation and was finally accomplished by a rhodium-catalyzed procedure[11] that required $[Rh_2(cap)_4]$ and *t*BuOOH as an oxidant (48% yield; Scheme 1). Other attempted methods to carry out this transformation (i.e. **4**→**11**) included the use of $Mn(OAc)_3$ and *t*BuOOH[12] (see Table 1 and Scheme 2) or bleach and *t*BuOOH,[13] both of which furnished the desired product, albeit in lower yields and with more cumbersome protocols. At this juncture, we had the opportunity to briefly explore the scope of the rhodium-catalyzed and other oxygenations of substituted cyclopentenes such as **4** and related compounds and discovered an interesting and potentially useful regioselectivity effect. While methyl ester **4** and its Weinreb amide sibling **4a** reacted with *t*BuOOH and $[Rh_2(cap)_4]$ catalyst to afford the disubstituted enones **11** and **11a**,

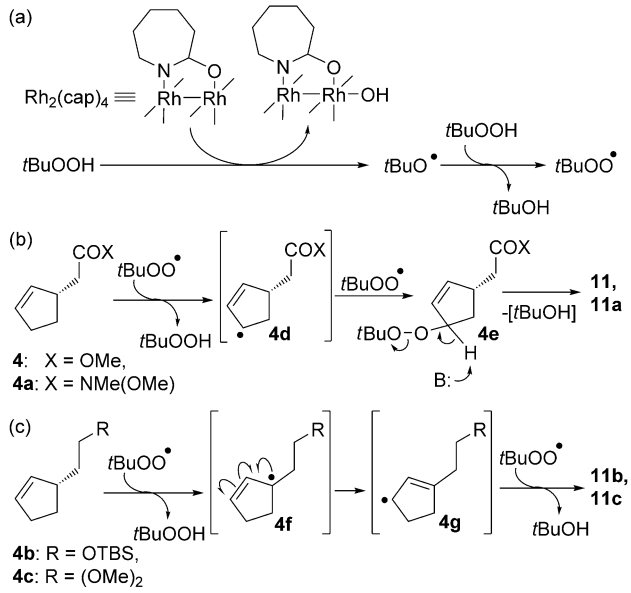
Table 1: Regioselective C–H activation/oxygenation of substituted cyclopentenes.[a]

Entry	Substrate	Catalyst	Product	Yield [%][d]
1	 **4**	$[Rh(cap)_4]$[b]	 **11**	48
2		$Mn(OAc)_3$[c]		35
3	 **4a**	$[Rh(cap)_4]$[b]	 **11a**	41
4		$Mn(OAc)_3$[c]		37
5	 **4b**	$[Rh(cap)_4]$[b]	 **11b**	63
6		$Mn(OAc)_3$[c]		61
7	 **4c**	$[Rh(cap)_4]$[b]	 **11c**	45
8		$Mn(OAc)_3$[c]		39

[a] Reactions were carried out on 1.0 mmol scale at 25 °C. Reagents and conditions: [b] $[Rh_2(cap)_4]$ (0.01 equiv), *t*BuOOH (5.0 equiv), K_2CO_3 (0.5 equiv), CH_2Cl_2, 1.5 h; then $[Rh_2(cap)_4]$ (0.01 equiv), *t*BuOOH (5.0 equiv), 1.5 h; [c] $Mn(OAc)_3$ (0.25 equiv), *t*BuOOH (4.0 equiv), M.S. 3Å, EtOAc, 24 h. [d] Yields refer to chromatographically isolated and spectroscopically pure products. M.S. = molecular sieves.



Scheme 1. Synthesis of cyclopentenone fragment **2**. Reagents and conditions: a) DIBAL-H (1 M in CH_2Cl_2, 1.2 equiv), CH_2Cl_2, 0 °C, 30 min; b) Ac_2O (2.0 equiv), Et_3N (2.5 equiv), DMAP (0.1 equiv), CH_2Cl_2, 0→25 °C, 18 h, 62% for two steps; c) dimethyl malonate (3.0 equiv), $[\eta^3\text{-}C_3H_5PdCl]_2$ (0.005 equiv), (*S*,*S*)-DACH-phenyl Trost ligand (0.015 equiv), Cs_2CO_3 (3.0 equiv), CH_2Cl_2, 25 °C, 3 h, 71%; d) KI (8.0 equiv), DMI/H_2O (10:1), 130 °C, 12 h, 94%; e) $[Rh_2(cap)_4]$ (0.01 equiv), *t*BuOOH (5.0 equiv), K_2CO_3 (0.5 equiv), CH_2Cl_2, 1.5 h, 25 °C; then $[Rh_2(cap)_4]$ (0.01 equiv), *t*BuOOH (5.0 equiv), 1.5 h, 25 °C, 48%; f) $CeCl_3\cdot 7H_2O$ (1.0 equiv), $NaBH_4$ (1.0 equiv), −30 °C, 10 min, 95%; g) DIBAL-H (1 M in CH_2Cl_2, 2.2 equiv), CH_2Cl_2, −78 °C, 45 min, 95%; h) $IPh_3P(CH_2)_5OPMB$ (2.5 equiv), NaHMDS (1 M in THF, 3.0 equiv), THF, −78→25 °C, 18 h, 79%; i) PCC (2.0 equiv), CH_2Cl_2, 25 °C, 3 h, 93%; j) TBSCl (1.5 equiv), imid. (3.0 equiv), CH_2Cl_2, 0→25 °C, 15 min; k) DIBAL-H (1 M in CH_2Cl_2, 1.1 equiv), CH_2Cl_2, −78 °C, 45 min; l) $IPh_3P(CH_2)_5OPMB$ (1.5 equiv), NaHMDS (1 M in THF, 2.0 equiv), THF, −78→25 °C, 6 h, 85% for three steps; m) TBAF (1 M in THF, 1.2 equiv), THF, 0→25 °C, 5 h, 91%. DACH-phenyl Trost ligand = 1,2-diaminocyclohexane-*N*,*N*′-*bis*(2′-diphenylphosphinobenzoyl); DIBAL-H = diisobutylaluminum hydride; DMAP = 4-dimethylaminopyridine; DMI = 1,3-dimethyl-2-imidazolidinone; DMM = dimethyl malonate; imid. = imidazole; NaHMDS = sodium *bis*(trimethylsilyl)-amide; PCC = pyridinium chlorochromate; PMB = *para*-methoxybenzyl; $[Rh_2(cap)_4]$ = dirhodium tetracaprolactamate; TBAF = tetrabutylammonium fluoride; TBS = *tert*-butyldimethylsilyl; THF = tetrahydrofuran.

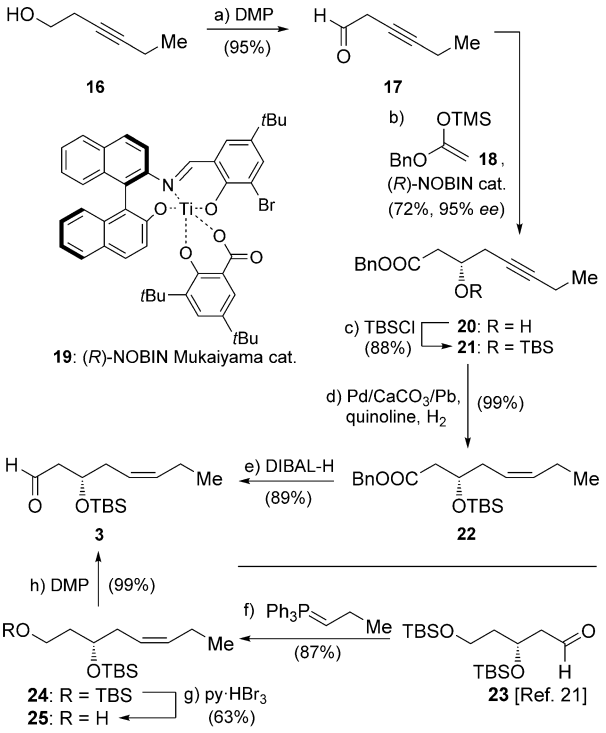


Scheme 2. Mechanistic rationale for the regioselective formation of enones **11** and **11a** and transposed enones **11b** and **11c** (see Table 1).

respectively (through intermediate peroxide species **4e**), the corresponding reduced substrates **4b** and **4c** behaved differently, leading instead to the trisubstituted enones **11b** and **11c**, respectively, in which the enone functionality had undergone transposition toward the side chain (see Table 1 and Scheme 2). This structural shift may be attributed to electronic effects and the radical nature of the oxygenation reactions, as depicted mechanistically in Scheme 2. Thus, reaction of $[Rh_2(cap)_4]$ with *t*BuOOH produces *t*BuOO• (see Scheme 2a),[9] initiating the reactions shown in Scheme 2b and c. Substrates **4** and **4a** carry an electron-withdrawing group at the β-position from the trisubstituted carbon atom on the cyclopentene ring that can exert a destabilizing effect on the corresponding tertiary radical at that position, thereby favoring the formation of the corresponding secondary radical **4d**[14] which leads to products **11** and **11a** via intermediate peroxide **4e** (see Scheme 2b). On the other hand, substrates **4b** and **4c** are not suffering from this predicament and, therefore, lead to the more stable tertiary radical **4f**, which undergoes rapid rearrangement to the less-hindered secondary radical species **4g**, whose facile reaction with *t*BuOO• leads to products **11b** and **11c** through the corresponding peroxide (see Scheme 2c). A similar mechanistic rationale may be applicable to the manganese-catalyzed processes shown in Table 1. These observations could be expanded to wider explorations in search of new synthetic methodologies.

Returning to the synthesis of advanced intermediate **2** (Scheme 1), enone **11** was further elaborated to allylic alcohol **12** by Luche reduction[15] ($NaBH_4$, $CeCl_3$, 95% yield, ca. 10:1 d.r., inconsequential) and then to hydroxy aldehyde **13** through reduction with DIBAL-H (2.2 equiv, 95% yield) in preparation for the pending Wittig olefination reaction. The latter reaction proceeded smoothly by generating the ylid from {5-[(4-methoxybenzyl)oxy]pentyl}-triphenylphosphonium iodide ($IPh_3P(CH_2)_5OPMB$; for preparation see the Supporting Information) and NaHMDS at −78 °C, and reacting it at low temperature (−78→25 °C) with hydroxy aldehyde **13**, furnishing, after oxidation with PCC, enone **2**[6] in 73% overall yield and good stereoselectivity ($Z{:}E \geq 10{:}1$, determined by ^{1}H NMR spectroscopic analysis). An alternative, slightly higher yielding, but longer sequence for the conversion of allylic alcohol **12** to enone **2** was also carried out (Scheme 1). Compound **12** was silylated (TBSCl, imid.) to afford the expected TBS-protected ether, which was subjected to reduction with DIBAL-H to give the corresponding aldehyde, whose reaction with the ylid generated from $IPh_3P(CH_2)_5OPMB$ and NaHMDS, as before, furnished bisolefin **14** ($Z{:}E \geq 10{:}1$) in 85% overall yield. Desilylation of **14** (TBAF, 91% yield) followed by PCC oxidation then led to enone **2** in 93% yield.

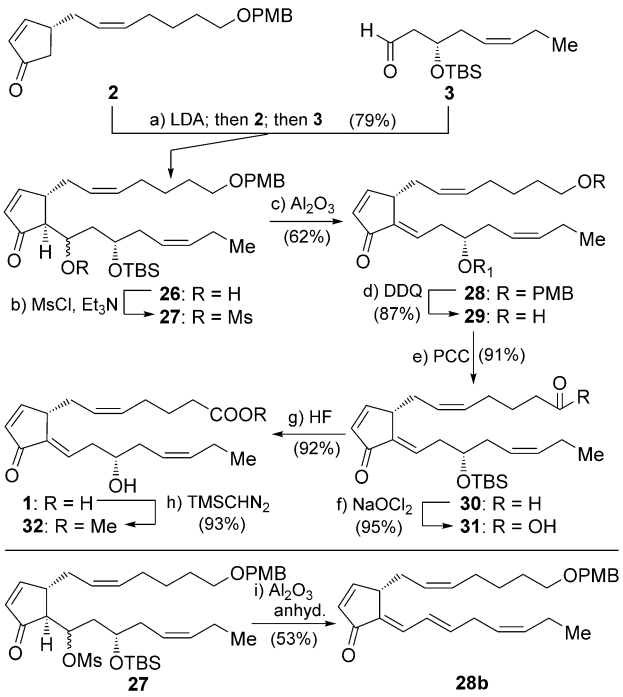
Scheme 3 depicts the catalytic asymmetric synthesis of the required aldehyde fragment **3**. Commercially available 3-hexynol (**16**) was oxidized with DMP to give hex-3-ynal (**17**,[16] 95% yield, crude, ≥95% purity by ^{1}H NMR analysis). Because of its rather labile nature, the latter was immediately,



Scheme 3. Synthesis of aldehyde fragment **3**. Reagents and conditions: a) DMP (1.3 equiv), CH_2Cl_2, 0→25 °C, 1.5 h, 95% crude; b) benzyl acetate trimethylsilyl acetal (**18**, 2.0 equiv), (*R*)-NOBIN Mukaiyama catalyst (**19**, 0.05 equiv), Et_2O, −78→−15 °C, 4 h; then aq. work-up; then TBAF (1 M in THF, 4.0 equiv), THF, 30 min, 72%; c) TBSCl (2.0 equiv), imid. (3.0 equiv), CH_2Cl_2, 25 °C, 3 h, 88%; d) Pd (5% on $CaCO_3$/Pb, 0.1 equiv), quinoline (1.0 equiv), H_2, EtOAc, 25 °C, 30 min, 99%; e) DIBAL-H (1 M in CH_2Cl_2, 1.3 equiv), CH_2Cl_2, −78→−25 °C, 1 h, 89%; f) $BrPh_3PPr$ (2.0 equiv), NaHMDS (2.0 equiv), 0 °C, 30 min; then **23**, −78→25 °C, THF, 2 h, 87%; g) py·HBr_3 (0.1 equiv), MeOH, −10 °C, 1.25 h, 63%; h) DMP (1.3 equiv), CH_2Cl_2, 0→25 °C, 2 h, 99%. DMP = 1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1*H*)-one; NOBIN = 2-amino-2′-hydroxy-1,1′-binaphthyl; py = pyridine; TMS = trimethylsilyl.

and without further purification, subjected to an enantioselective Mukaiyama aldol reaction employing the TMS-protected acetal (**18**)[17] of benzyl acetate and (*R*)-NOBIN Mukaiyama catalyst (**19**)[18] (5 mol%) to furnish, upon sequential aqueous work-up and exposure to TBAF, hydroxybenzyl ester **20** (72% yield, ≥95% *ee* by ^{19}F NMR spectroscopic analysis of the corresponding Mosher esters). The absolute configuration of **20** was confirmed by full Mosher ester analysis (see the Supporting Information). The hydroxy group of the latter intermediate was then protected as a TBS ether (TBSCl, imid., 88% yield), and the resulting acetylenic compound **21** was selectively reduced with Lindlar catalyst in the presence of quinoline under a hydrogen atmosphere to afford exclusively *Z*-olefin **22** in 99% yield. Selective reduction of the benzyl ester moiety of intermediate **22** with DIBAL-H then produced the targeted aldehyde fragment **3** in 89% yield. An alternative catalytic asymmetric route to aldehyde **3** was also developed, employing as a key step a Keck allylation[19] of 3-*tert*-butyl dimethylsilyloxy propanal with tri-*n*-butylstannane in the presence of catalytic amounts of (*S*)-BINOL[20] to provide, after silylation and ozonolysis, known aldehyde **23**[21] in high enantiomeric excess (95% *ee*, Scheme 3). Wittig olefination of **23** then furnished **24** (87% yield, *Z*:*E* ca. 8:1, chromatographically separable), which was desilylated (py·HBr_3, 63% yield) and oxidized (DMP, 99% yield) to afford aldehyde **3** via hydroxy compound **25** (Scheme 3).

With both fragments, cyclopentenone **2** and aldehyde **3**, readily available in their correct enantiomeric forms, their union through the planned aldol reaction and further elaboration of the product to Δ^{12}-PGJ_3 (**1**) became the next task. The generation of the enolate of **2** at −78 °C with LDA, followed by addition of **3** gave the expected aldol product **26** as a mixture of C13 epimers (ca. 3:1 d.r.) in 79% yield (Scheme 4).[6] While the stereochemical outcome of the aldol reaction at C13 was inconsequential, the exclusive stereoselectivity with regards to the stereocenter at C12 as a result of steric control was welcome. Mesylation of the C13-diastereomeric mixture **26** (MsCl, Et_3N) followed by treatment of the resulting mesylates (as a mixture or individually) with Al_2O_3[6] (as purchased, presumably containing traces of water) produced exclusively the *E*-Δ^{12}-configurational isomer **28**[22] in 62% overall yield for the two steps. It should be noted that the presence of moisture in the Al_2O_3 is essential for the success of this reaction, as employment of anhydrous Al_2O_3 (obtained by heating commercially available reagent at 400 °C under vacuum) under the same conditions led to double elimination from mesylate TBS ether **27** to afford pentaene **28b** (53% yield; see Scheme 4). All that remained now to reach the coveted Δ^{12}-PGJ_3 (**1**) was the elaboration of the functional group at C1 to the desired carboxylic acid moiety and the removal of the TBS group. The former task was most efficiently accomplished through the sequential use of DDQ (to remove the PMB group, **29**, 87% yield), PCC (to convert the resulting hydroxy group to the aldehyde, **30**, 91% yield), and $NaClO_2$ (Pinnick oxidation,[6,23] to oxidize the latter moiety to the carboxylic acid group, **31**, 95% yield). Finally, desilylation of the hydroxy group at C15 of the resulting precursor (**31**) with aqueous HF furnished Δ^{12}-PGJ_3 (**1**) in



Scheme 4. Coupling and completion of the synthesis of Δ^{12}-PGJ_3 (**1**). Reagents and conditions: a) LDA (2.0 equiv); then **2** (1.0 equiv); then **3** (1.2 equiv), THF, −78 °C, 30 min, 79%; b) MsCl (5.0 equiv), Et_3N (10 equiv), CH_2Cl_2, 0 °C, 5 min; c) Al_2O_3 (21 equiv), CH_2Cl_2, 25 °C, 8 h, 62% for two steps; d) DDQ (1.5 equiv), CH_2Cl_2/H_2O (16:1), 0 °C, 45 min; e) PCC (2.0 equiv), CH_2Cl_2, 25 °C, 2 h; f) $NaClO_2$ (1.5 equiv), NaH_2PO_4 (1.5 equiv), 2-methyl-2-butene (10 equiv), *t*BuOH/H_2O (4:3), 25 °C, 30 min, 75% for three steps; g) HF (50% aq, 50 equiv), MeCN, 0 °C, 45 min, 92%; h) $TMSCHN_2$ (2 M in Et_2O), C_6H_6/MeOH (3:2), 25 °C, 30 min, 93%; i) Al_2O_3 anhyd. (30 equiv), CH_2Cl_2, 25 °C, 1 h, 53%. DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone; LDA = lithium diisopropylamide.

92% yield. Δ^{12}-PGJ_3 methyl ester (**32**) was also prepared by treatment with trimethylsilyldiazomethane (93% yield) for the purposes of more convenient characterization and biological evaluation. Synthetic Δ^{12}-PGJ_3 (**1**) proved identical with the authentic substance by HPLC, UV spectroscopy, and mass spectrometry and was found to be equipotent against chronic myelogenous leukemia (CML) stem cells. ^{1}H NMR spectroscopic analysis of a small authentic sample confirmed its identity to the synthetic material.[24]

The described chemistry renders Δ^{12}-prostaglandin J_3 (Δ^{12}-PGJ_3, **1**) readily available for thorough biological and pharmacological investigations and opens the way for analogue design, synthesis, and biological evaluation of this important ω-3 series of eicosanoids. It may also provide inspiration and the foundation for method development in the field of regioselective C–H activation/functionalization of appropriately substituted olefinic substrates to produce useful chemical building blocks. Further research in both areas is currently in progress in our laboratory.

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