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Total Synthesis |*Hot Paper*|

Total Synthesis of Δ^{12}-Prostaglandin J_3: Evolution of Synthetic Strategies to a Streamlined Process

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Abstract: The total synthesis of Δ^{12}-prostaglandin J_3 (Δ^{12}-PGJ_3, **1**), a reported leukemia stem cell ablator, through a number of strategies and tactics is described. The signature cross-conjugated dienone structural motif of **1** was forged by an aldol reaction/dehydration sequence from key building blocks enone **13** and aldehyde **14**, whose lone stereocenters were generated by an asymmetric Tsuji–Trost reaction and an asymmetric Mukaiyama aldol reaction, respectively. During this program, a substituent-governed regioselectivity pattern for the Rh-catalyzed C–H functionalization of cyclopentenes and related olefins was discovered. The evolution of the synthesis of **1** from the original strategy to the final streamlined process proceeded through improvements in the construction of both fragments **13** and **14**, exploration of the chemistry of the hitherto underutilized chiral lactone synthon **57**, and a diastereoselective alkylation of a cyclopentenone intermediate. The described chemistry sets the stage for large-scale production of Δ^{12}-PGJ_3 and designed analogues for further biological and pharmacological studies.

Introduction

The search for cytotoxic agents against cancer stem cells (CSCs) has received increasing attention from the scientific community.[1] Although they represent only a small subpopulation of cancer cells, CSCs are notoriously resistant toward conventional therapies driving growth, proliferation, and relapse.[2] In 2011, Paulson and Prabhu reported the isolation of Δ^{12}-prostaglandin J_3 (Δ^{12}-PGJ_3, **1**, Figure 1) and 15-deoxy-$\Delta^{12,14}$-prostaglandin J_3 (15d-PGJ_3, **2**, Figure 1)[3] from endogenous metabolites of eicosapentaenoic acid (EPA, **5**, Figure 2), the dietary fish oil ω-3 polyunsaturated fatty acid. Δ^{12}-PGJ_3 was claimed to selectively induce apoptosis in leukemia stem cells (LSCs) in in vitro studies (IC_{50} value ~12 nM) with no significant effects on normal hematopoietic stem cells.[3] In addition, intraperitoneal administration of Δ^{12}-PGJ_3 to two infected murine models successfully eradicated LSCs and restored normal physiological parameters.[3] Other favorable properties attributed to Δ^{12}-PGJ_3 include reasonable stability and bioavailability and minimal hypersensitivity.[4] These results elevate Δ^{12}-PGJ_3 (**1**) to a lead compound warranting further investigation in search of new therapies for the treatment of acute and chronic myelogenous leukemia (AML and CML).[3–5]

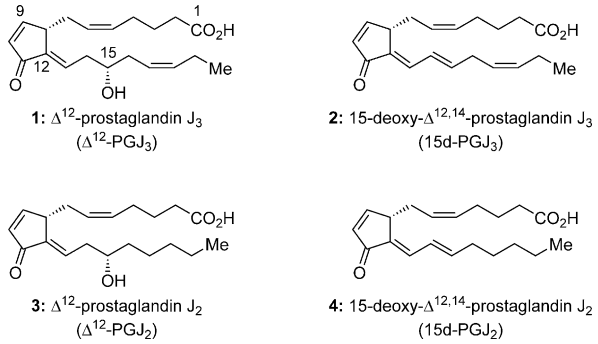

Figure 1. Molecular structures of Δ^{12}-prostaglandin J_3 (Δ^{12}-PGJ_3) and related natural products.

The structure of Δ^{12}-PGJ_3 (**1**), isolated in only microgram quantities, was proposed based on mass spectrometric and UV spectroscopic measurements and biosynthetic analogy considerations to the known J_2 series prostaglandins [Δ^{12}-PGJ_2 (**3**) and 15d-PGJ_2 (**4**) (Figure 1)].[3,6,7] Specifically, it was surmised that the J_3 series of PGJs [PGJ_3 (**7**), Δ^{12}-PGJ_3 (**1**) and 15d-PGJ_3 (**2**), see Figure 2a] are the biosynthetic downstream products of EPA (**5**)-derived prostaglandin D_3 [PGD_3 (**6**), Figure 2a] formed through dehydration, isomerization, and further dehydration (Figure 2).[3] A similar biosynthetic pathway was known to account for the formation of 15d-PGJ_2 (**4**) from arachidonic acid (ARA, **8**, see Figure 2b).[6] Despite their structural resemblance, the ARA- and EPA-derived PGJs might act differently on the p53 tumor suppression protein.[3] Whereas 15d-PGJ_2 (**4**) is known to functionally inactivate p53, the proapoptotic effect

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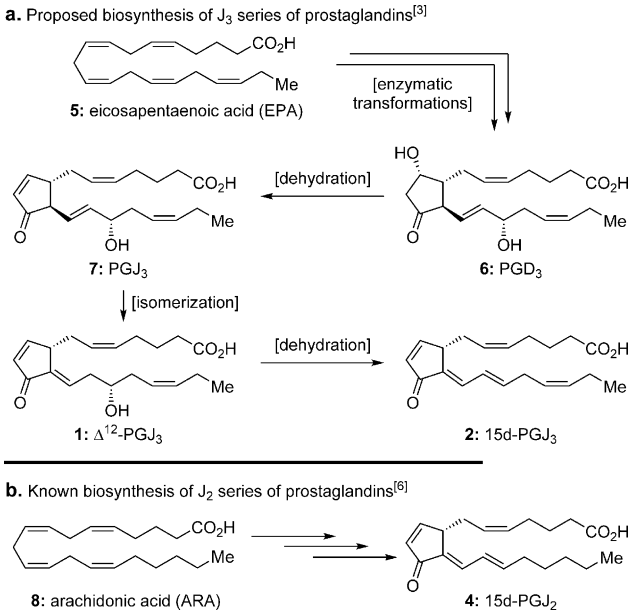


Figure 2. Biosynthesis of the a) J_3 and b) J_2 series of prostaglandins.[3,6]

of Δ^{12}-PGJ_3 (**1**) has been suggested to arise from activation of the same protein.[3]

The most prominent structural feature of prostaglandins **1**–**4** (Figure 1) is the cross-conjugated dienone structural motif, which is also shared by other natural and designed prostanoids, such as **9**–**12** (Figure 3).[8–11] Some of these have been shown to react with endogenous nucleophiles (e.g., glutathione, protein cysteine residues) selectively at the endocyclic double bond (rather than the exocyclic double bond).[12] Computational studies attributed this selectivity to a higher LUMO coefficient and greater distribution of positive charge at the endocyclic β-carbon of the enone system.[12]

Due to their natural scarcity and important biological properties, the prostaglandins have been the target of numerous total syntheses,[13] with one of the challenges being the installment of substituents on the conformationally flexible five-membered ring. Such endeavors not only enabled the structural elucidation of these often labile secondary metabolites, but also facilitated their biological investigation by rendering them readily available. Some of these studies were also accompanied by developments in synthetic methodologies, such as the Corey–Bakshi–Shibata asymmetric reduction[14] and catalytic asymmetric Diels–Alder reaction,[15] that desirably impacted organic synthesis in general.

Intrigued by the remarkable antileukemic properties reported for Δ^{12}-PGJ_3, we initiated a program directed toward its total synthesis. In 2014, we reported the first total synthesis of this molecule, which allowed its structural confirmation.[16] Herein, we provide a detailed account of our work, including the development of several distinct strategies to access and assemble the various building blocks employed, culminating into a short and efficient process for the synthesis of this target molecule [Δ^{12}-PGJ_3 (**1**)] that could provide it in large amounts and be applicable to the construction of its analogues as well as other related prostanoids.[17]

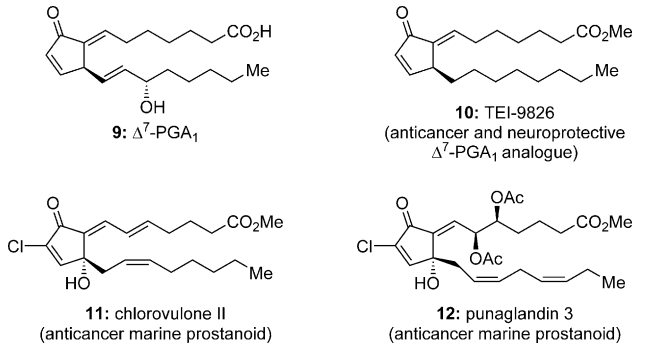


Figure 3. Selected prostanoids with cross-conjugated dienone structural motifs.

Results and Discussion

First-generation synthesis: Application of asymmetric Tsuji–Trost alkylation and asymmetric Mukaiyama aldol reaction

In light of the reactive nature of the 2-alkylidene cyclopentenone moiety, some of the previous approaches toward these types of prostaglandins involved masked forms of this structural unit, which were unmasked in the final step of the syntheses (e.g., via retro-Diels–Alder reaction,[18] Saegusa–Ito oxidation,[17g] bis-allylic alcohol oxidation[17b]). We decided to pursue a more straightforward approach involving the convergent union of cyclopentenone **13** and β-siloxyaldehyde **14** via aldol reaction/dehydration as indicated retrosynthetically in Figure 4. Although such a sequence would generate the cross-conjugated dienone directly, the stability of the C15 bis-homoallylic alcohol [as opposed to the homoallylic alcohol in Δ^{12}-PGJ_2 (**3**, Figure 1)] under the proposed reaction conditions could not be assumed a priori. Both fragments, **13** and **14**, contain a lone stereocenter that was to be introduced asymmetrically. In contrast to the strategies employed in Kobayashi's synthesis

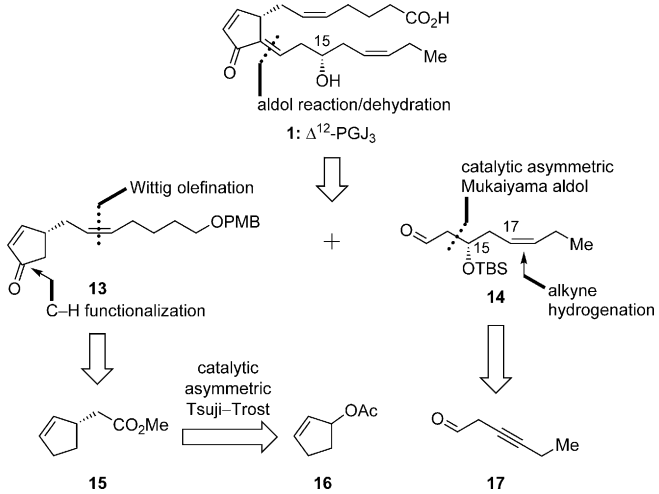
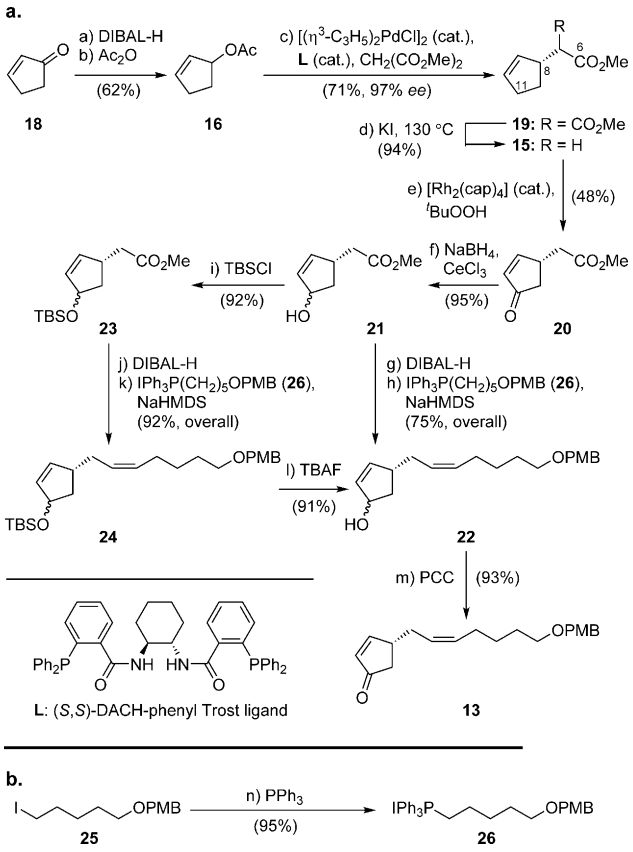


Figure 4. First-generation retrosynthetic analysis of Δ^{12}-PGJ_3 (**1**). PMB = *para*-methoxybenzyl; TBS = *tert*-butyldimethylsilyl.

of Δ^{12}-PGJ$_2$ (**3**),[17d,e] we envisioned derivation of enone **13** from cyclopentene **15** through Wittig olefination and regioselective C–H functionalization (Figure 4). The latter intermediate could be obtained by catalytic asymmetric Tsuji–Trost alkylation of racemic acetate **16**. The C15 stereocenter (PGJ numbering) of the β-siloxyaldehyde fragment **14** was expected to arise from an asymmetric Mukaiyama aldol reaction of hex-3-ynal (**17**, Figure 4). Subsequent (*Z*)-selective alkyne hydrogenation would then install the C17–C18 olefinic bond, a distinctive structural feature of the J$_3$ series prostaglandins.

The synthesis of cyclopentenone fragment **13** began with the preparation of racemic acetate **16** following a modified literature procedure,[19] as outlined in Scheme 1a. Thus, reduction of commercially available 2-cyclopentenone (**18**) (DIBAL-H) followed by acetylation (Ac_2O, Et_3N, DMAP) gave volatile acetate **16** in 62% overall yield. Asymmetric Tsuji–Trost allylic alkylation[20] of racemic **16** with the enolate of dimethyl malonate (generated through in situ deprotonation with Cs_2CO_3) proceeded smoothly in the presence of $[(\eta^3\text{-}C_3H_5)PdCl]_2$ (0.5 mol%) and (*S*,*S*)-DACH-phenyl Trost ligand (1.5 mol%), furnishing dimethyl ester **19** in 71% yield and 97% *ee*. The absolute configuration and *ee* were deduced from comparison of the optical rotation with that of the known enantiomer (i.e., antipode of **19**).[20b] Heating a mixture of diester **19** and KI in wet DMI at 130 °C resulted in mono decarboxylation, affording ester **15** in excellent yield (94%).

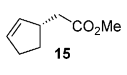
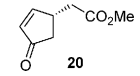
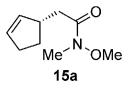
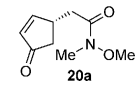
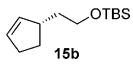
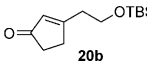
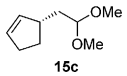
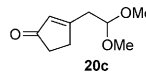
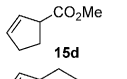
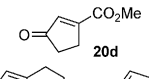
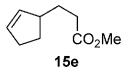
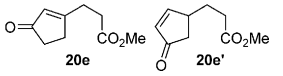
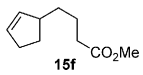
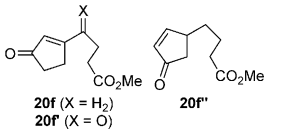
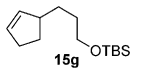
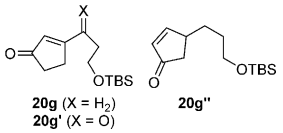
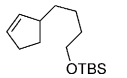
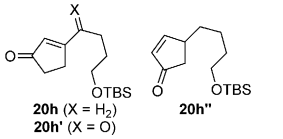
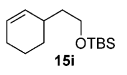
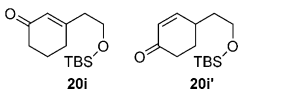
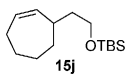
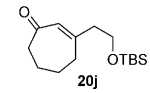
With ester **15** in hand, we proceeded to examine the C–H functionalization/oxidation step with the hope that the C11 methylene could be oxidized in preference to the C8 methine (PGJ numbering). It was found after systematic experimentation (see Table 1) that the combination of *t*BuOOH and catalytic amounts of $[Rh_2(cap)_4]$, a catalyst introduced by Doyle et al.,[21] produced the desired regioisomer **20** in 48% yield. Other common conditions [e.g., SeO_2, *t*BuOOH–PDC,[22] *t*BuOOH–bleach,[23] $Mn(OAc)_3$ with or without O_2 atmosphere[24]] proved to be inferior. During our earlier investigations,[16] we had also studied the C–H oxidation on alternative substrates with either a TBS-protected primary alcohol (**15b**, entry 3, Table 1) or a dimethyl acetal (**15c**, entry 4, Table 1), both of which could be converted, in principle, to the C6 aldehyde for the upcoming Wittig olefination (vide infra). However, under identical conditions, these substrates provided the trisubstituted enones **20b** and **20c**, respectively (entries 3 and 4, Table 1), in which the C–H oxidation occurred with concomitant olefin transposition.[25] Intrigued by this observation, we prepared a series of substrates with different ring sizes and side-chain functionalities (**15**, **15a**–**j**, Table 1) and subjected them to the action of *t*BuOOH in the presence of catalytic amounts of $[Rh_2(cap)_4]$ (conditions A[21a]) or $Mn(OAc)_3$ (conditions B[24a]). As it turned out, most of the substituted cyclopentenes examined (**15b**–**j**, entries 3–11, Table 1) afforded the transposed enones (**20b**–**j**) as the major or exclusive product. On the other hand, substrates **15** and **15a** (entries 1 and 2), in which a side-chain electron-withdrawing group is connected to the five-membered ring through a single methylene bridge, underwent direct allylic oxidation without migration of the double bond.



Scheme 1. Synthesis of cyclopentenone fragment **13**. Reagents and conditions: a) DIBAL-H (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 to 25 °C, 18 h, 62% for the two steps; c) dimethyl malonate (3.0 equiv), $[(\eta^3\text{-}C_3H_5)PdCl]_2$ (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% (97% *ee*); d) KI (8.0 equiv), DMI/H_2O (10:1), 130 °C, 12 h, 94%; e) $[Rh_2(cap)_4]$ (0.005 equiv), *t*BuOOH (5.0 equiv), K_2CO_3 (0.5 equiv), CH_2Cl_2, 25 °C, 1.5 h; then $[Rh_2(cap)_4]$ (0.005 equiv), *t*BuOOH (5.0 equiv), 25 °C, 1.5 h, 48%; f) $CeCl_3{\cdot}7H_2O$ (1.0 equiv), $NaBH_4$ (1.0 equiv), −30 °C, 10 min, 95%; g) DIBAL-H (2.2 equiv), CH_2Cl_2, −78 °C, 45 min; h) $IPh_3P(CH_2)_5OPMB$ (**26**) (2.5 equiv), NaHMDS (3.0 equiv), THF, −78 to 25 °C, 18 h, 75% for the two steps; i) TBSCl (1.5 equiv), imid. (3.0 equiv), CH_2Cl_2, 0 to 25 °C, 15 min, 92%; j) DIBAL-H (1.1 equiv), CH_2Cl_2, −78 °C, 45 min; k) $IPh_3P(CH_2)_5OPMB$ (**26**) (1.5 equiv), NaHMDS (2.0 equiv), THF, −78 to 25 °C, 6 h, 92% for the two steps; l) TBAF (1.2 equiv), THF, 0 to 25 °C, 5 h, 91%; m) PCC (2.0 equiv), CH_2Cl_2, 25 °C, 3 h, 93%; n) PPh_3 (5.0 equiv), toluene, reflux, 18 h, 95%. DACH-phenyl Trost ligand = *N*,*N*′-(1*S*,2*S*)-cyclohexane-1,2-diylbis[2-(diphenylphosphino)benzamide]; DIBAL-H = diisobutylaluminum hydride; DMAP = 4-dimethylaminopyridine; DMI = 1,3-dimethyl-2-imidazolidinone; imid. = 1*H*-imidazole; NaHMDS = sodium bis(trimethylsilyl)amide; PCC = pyridinium chlorochromate; $[Rh_2(cap)_4]$ = dirhodium tetracaprolactamate; TBAF = tetra-*n*-butylammonium fluoride.

A mechanistic rationale was proposed to account for the above heterogeneity in regioselectivity as shown in Figure 5. Thus, *t*BuOO$^{\bullet}$, the species responsible for hydrogen atom abstraction, is generated through the reaction of *t*BuOOH with $[Rh_2(cap)_4]$ (Figure 5 a).[21a] Due to its moderate reactivity, reactions of *t*BuOO$^{\bullet}$ with aliphatic C–H bonds are known to be highly selective, resulting in generation of the most stable radicals.[26] In the case of 3-substituted cyclopentenes (**A**, Figure 5 b), abstraction of the tertiary allylic hydrogen leads to allylic radical **B**, whose reaction with another equivalent of

Table 1. Regioselective allylic oxidation of substituted cyclopentenes and related cycloalkenes with $[Rh_2(cap)_4]$ (cat.) and *t*BuOOH (**A**) or $Mn(OAc)_3$ (cat.) and *t*BuOOH (**B**).[a]

Entry	Substrate	Product(s)	Yield [%][b]
1	 **15**	 **20**	A: 48 B: 35
2	 **15a**	 **20a**	A: 41 B: 37
3	 **15b**	 **20b**	A: 63 B: 61
4	 **15c**	 **20c**	A: 45 B: 39
5	 **15d**	 **20d**	A: 38 B: 47
6	 **15e**	 **20e** **20e'**	A: 26/13 B: 20/0
7	 **15f**	 **20f** (X = H_2) **20f'** (X = O) **20f''**	A: 20/14/16 B: 22/6/8
8	 **15g**	 **20g** (X = H_2) **20g'** (X = O) **20g''**	A: 32/9/13 B: 6/7/11
9	 **15h**	 **20h** (X = H_2) **20h'** (X = O) **20h''**	A: 20/11/7 B: 21/9/11
10	 **15i**	 **20i** **20i'**	A: 43/10 B: 34/11
11	 **15j**	 **20j**	A: 64 B: 27

[a] Reactions were carried out on 1.0 mmol scale at 25 °C. Conditions A: $[Rh_2(cap)_4]$ (0.005 equiv), *t*BuOOH (5.0 equiv), K_2CO_3 (0.5 equiv), CH_2Cl_2, 1.5 h; then $[Rh_2(cap)_4]$ (0.005 equiv), *t*BuOOH (5.0 equiv), 1.5 h. Conditions B: $Mn(OAc)_3$ (0.25 equiv), *t*BuOOH (4.0 equiv), 3 Å MS, EtOAc, 24 h. [b] Yields refer to chromatographically isolated and spectroscopically pure products. In cases where multiple products were generated, yields were shown in the same order as the listed structures.

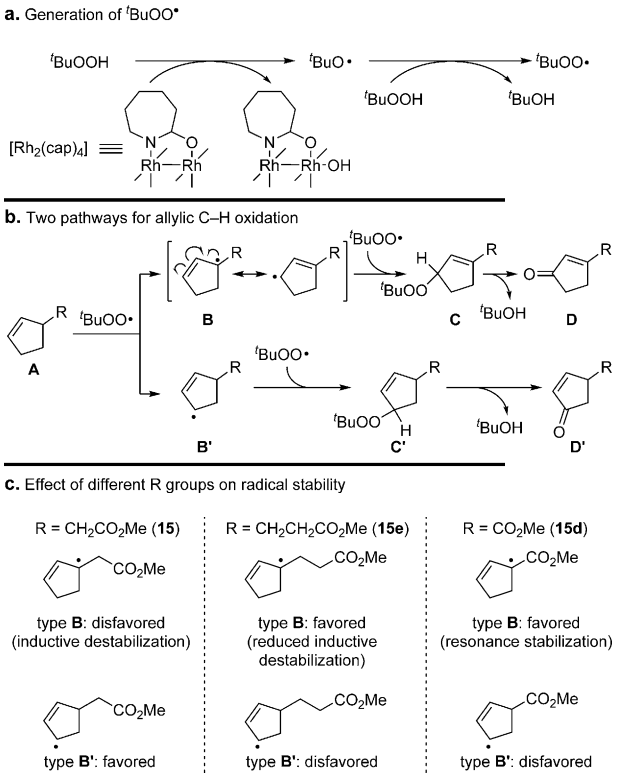


Figure 5. Mechanistic rationale for the regioselective C–H oxidation.

*t*BuOO• (or its Rh-bound counterpart) at the more sterically accessible site furnishes peroxide **C**. Elimination of *t*BuOH from the latter then affords the observed transposed enone product **D** (Figure 5b).

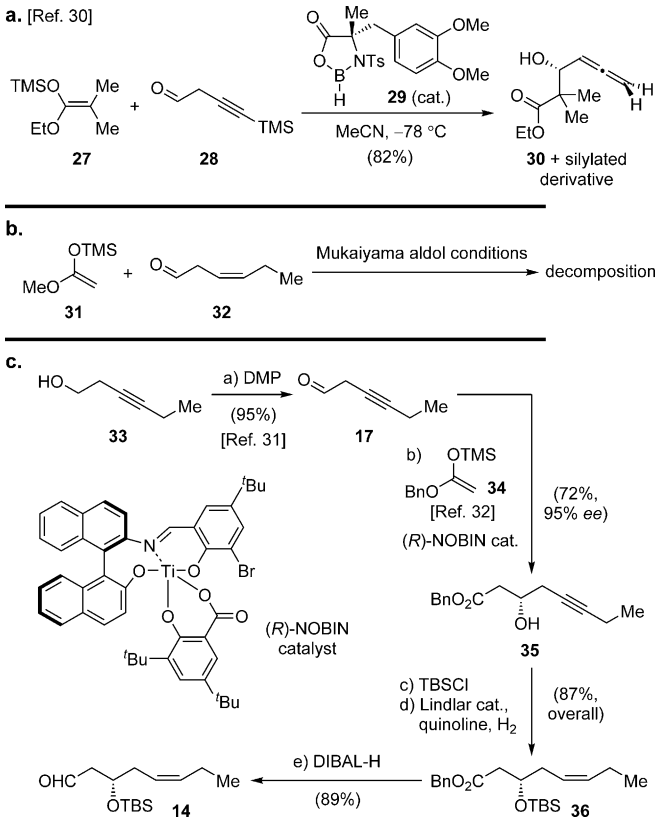
Alternatively, formation of the isomeric radical **B′** could occur by removal of the secondary allylic hydrogen. Subsequent C–O bond formation and elimination would give rise to enone **D′** via the intermediacy of peroxide **C′** (Figure 5b). The ratio of the final products **D** and **D′** depends on the relative stability of radicals **B** and **B′**, which in turn is determined by the nature of the R group.[27] In substrate **15** (R = CH_2CO_2Me, Figure 5c), the electron-withdrawing ester moiety inductively destabilizes the type **B** radical, thereby leading to exclusive formation of enone **20** (entry 1, Table 1). Such inductive effect, however, is markedly attenuated in the homologated substrate **15e** (R = $CH_2CH_2CO_2Me$, Figure 5c), resulting in the selective formation of transposed enone **20e** (entry 6, Table 1) via the more substituted (hence, more stable) tertiary allylic radical **B**. While cyclopentene **15d** (R = CO_2Me, Figure 5c) also gives the transposed enone **20d** (entry 5, Table 1), it represents a different scenario, in which the tertiary allylic radical **B** is further stabilized through extended conjugation with the ester moiety (Figure 5c). Regioselectivities for other substrates in Table 1 could be likewise explained. Switching the catalyst from $[Rh_2(cap)_4]$ to $Mn(OAc)_3$ gives the same trend in selectivity, albeit in most cases with a decrease in yield (conditions B, Table 1). Interestingly and as shown in Table 1 (entries 7–9), bis-oxidation was observed in some cases leading to conjugated diketones **20f′**–**20h′** as minor products.

Returning to the synthesis of the targeted enone **13** (Scheme 1a), Luche reduction ($NaBH_4$, $CeCl_3{\cdot}7H_2O$)[28] of enone **20** afforded hydroxyl ester **21** (95%, ca. 10:1 d.r., inconsequential), whose partial reduction with DIBAL-H gave the corresponding hydroxyl aldehyde (not shown), thus setting the stage for the Wittig olefination. In the event, treatment of 2.5 equivalents of ω-(*para*-methoxybenzyloxy)pentyltriphenylphosphonium iodide [$IPh_3P(CH_2)_5$-OPMB, **26**; synthesized in one step from iodide **25**,[29] Scheme 1b], with NaHMDS at 0 °C, followed by addition of the above hydroxyl aldehyde at −78 °C and reaction at 25 °C for 12 h, furnished the desired (*Z*)-olefin **22** in high yield (75% from **21**) and selectivity [(*Z*):(*E*) ≥ 10:1 as

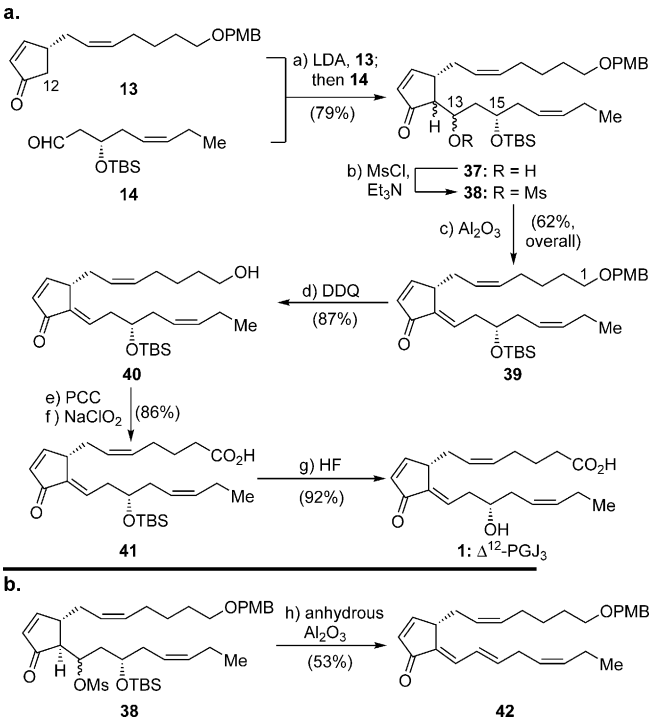
judged by NMR spectroscopic analysis]. Finally, the coveted enone fragment **13** was obtained after PCC oxidation of allylic alcohol **22** (93%).[17d,e] An alternative synthesis of **22** from **21** involved initial silylation of the latter (TBSCl, 92%), followed by DIBAL-H reduction and Wittig olefination (92% for the two steps), and a final desilylation (TBAF, 91%). Despite its greater step count, this four-step sequence provided alcohol **22** in slightly higher overall yield (77% vs. 75%), and required less phosphonium salt **26** for the olefination step (1.5 equiv vs. 2.5 equiv).

Construction of the β-siloxyaldehyde fragment **14** (Figure 4) required an asymmetric Mukaiyama aldol reaction between a β,γ-unsaturated aldehyde (e.g., **17**, Figure 4) and a suitable two-carbon unit. However, the inherent lability of the β,γ-unsaturated aldehyde system as well as its propensity to undergo isomerization cast doubt on the feasibility of this transformation. Indeed, Shao and Huang reported that treatment of silyl ketene acetal **27** in the presence of boron catalyst **29** furnished only the allenyl alcohol **30** (together with its silylated derivative) (Scheme 2a).[30] Moreover, our initial attempts to achieve the desired Mukaiyama aldol using (*Z*)-hex-3-enal (**32**) proved fruitless due to extensive decomposition (Scheme 2b). After much experimentation, it was eventually found that the projected transformation could be accomplished by mixing hex-3-ynal [**17**, freshly prepared by DMP-oxidation of 3-hexyn-1-ol (**33**),[31] Scheme 2c] with TMS-protected acetal **34**[32] and the (*R*)-NOBIN catalyst developed by Carreira and co-workers.[33] The crude silyl aldolate was then treated with TBAF to afford homopropargylic alcohol **35** in 72% yield and 95% *ee* (determined by ^{19}F NMR analysis of its Mosher ester derivative). A full Mosher ester analysis[34] of alcohol **35** revealed the absolute configuration of its chiral center to be (*S*) (as drawn in Scheme 2c; see Supporting Information for details). Protection of the newly generated alcohol in **35** (TBSCl) followed by partial reduction of the alkyne (H_2, Lindlar cat., quinoline) provided (*Z*)-alkene **36** as the only geometrical isomer (87% over the two steps). The benzyl ester moiety was then reduced with DIBAL-H to give the desired β-siloxyaldehyde **14** (89%).

The final stages of the synthesis of Δ^{12}-PGJ$_3$ (**1**) are summarized in Scheme 3. Thus, regioselective deprotonation of cyclopentenone **13** (1.0 equiv) at the C12 position was achieved with LDA at −78 °C (Scheme 3a). Addition of the aldehyde fragment **14** (1.2 equiv) to the so generated enolate at −78 °C followed by stirring for 30 min at the same temperature furnished the desired product **37** (79%) as an inconsequential



Scheme 2. Synthesis of aldehyde fragment **14**. a) DMP (1.3 equiv), CH_2Cl_2, 0 to 25 °C, 1.5 h, 95% crude; b) BnO(TMSO)C=CH_2 (**34**, 2.0 equiv), (*R*)-NOBIN catalyst (0.05 equiv), Et_2O, −78 to −15 °C, 4 h; then aq. work-up; then TBAF (4.0 equiv), THF, 30 min, 72%, 95% *ee*; c) TBSCl (2.0 equiv), imid. (3.0 equiv), CH_2Cl_2, 25 °C, 3 h; d) Pd (5% on $CaCO_3$/Pb, Lindlar cat., 0.1 equiv), quinoline (1.0 equiv), H_2, EtOAc, 25 °C, 30 min, 87% for the two steps; e) DIBAL-H (1.3 equiv), CH_2Cl_2, −78 to −25 °C, 1 h, 89%. DMP = Dess–Martin periodinane; NOBIN = 2-amino-2′-hydroxy-1,1′-binaphthyl; TMS = trimethylsilyl.



Scheme 3. Coupling of fragments **13** and **14** and completion of the synthesis of Δ^{12}-PGJ$_3$ (**1**). Reagents and conditions: a) LDA (2.0 equiv), **13** (1.0 equiv), THF, −78 °C, 20 min; then **14** (1.2 equiv), −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 the two steps; d) DDQ (1.5 equiv), CH_2Cl_2/H_2O (16:1), 0 °C, 45 min, 87%; 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, 86% for the three steps; g) HF (50% aq., 50 equiv), MeCN, 0 °C, 45 min, 92%; h) anhydrous Al_2O_3 (30 equiv), CH_2Cl_2, 25 °C, 1 h, 53%. DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone; LDA = lithium diisopropylamide; Ms = methanesulfonyl.

pair of C13 epimers (ca. 3:1 d.r.).[17d,e] Brief exposure of the aldol product **37** (mixture of epimers) to a mixture of MsCl and Et_3N gave the corresponding mesylate (**38**, ca. 3:1 d.r.), which, even in the presence of excess Et_3N, did not undergo β-elimination in the reaction medium. The latter transformation required the action of commercial neutral Al_2O_3 (Brockmann I, 50–200 μm, used as received) and led to the pivotal cross-conjugated dienone system (see **39**, Scheme 3a, 62% for the two steps), while leaving the C15-OTBS group intact.[17d,e] Two aspects of this elimination reaction deserve further comment. First, both diastereomers of mesylate **38** selectively produced the desired, and most likely the more thermodynamically stable (*E*)-Δ^{12}-isomer,[35] although there was a notable difference in the rate of elimination. Second, due to its hygroscopic nature, commercial Al_2O_3 is likely to contain a small amount of moisture. This factor turned out to be essential for the success of this reaction as anhydrous Al_2O_3 (obtained by heating the commercial reagent at 400 °C under vacuum for 5 min prior to the reaction) gave only the double elimination product **42** in 53% yield, as shown in Scheme 3b.

At this stage, the PMB protecting group in dienone **39** (Scheme 3a), which had served well in its role to cap the C1 hydroxyl group, was cleaved with DDQ (87%). The resulting primary alcohol **40** was converted to the corresponding carboxylic acid **41** through a two-step oxidation process [PCC; then $NaClO_2$ (Pinnick oxidation),[36] 86%].[17d,e] The final desilylation was then accomplished with 50% aqueous HF in MeCN, furnishing Δ^{12}-PGJ$_3$ (**1**) in 92% yield after careful purification. The UV, HPLC, and mass spectrum were in agreement with those of the biosynthetically generated Δ^{12}-PGJ$_3$ (**1**) by the Prabhu–Paulson team.[3a,16] Furthermore, we were able to obtain a ^{1}H NMR spectrum of a minute amount of a sample of Δ^{12}-PGJ$_3$ (**1**) from these investigators, comparison of which with that of synthetic Δ^{12}-PGJ$_3$ (**1**) revealed the identity of the two samples (see Supporting Information of reference [16]). Next, a stability test for Δ^{12}-PGJ$_3$ (**1**) was carried out and, interestingly, the natural Δ^{12}-PGJ$_3$ (**1**) was stable when stored neat at 25 °C with only small amounts of degradation products observed after one week (as judged by ^{1}H and ^{13}C NMR spectroscopic analysis). When dissolved in unneutralized $CDCl_3$, however, Δ^{12}-PGJ$_3$ (**1**) gave notable decomposition after a few days, likely owing to the residual acid present in the NMR solvent.

Improved syntheses of β-siloxyaldehyde fragment 14

Our first-generation synthesis of Δ^{12}-PGJ$_3$ (**1**) rendered this scarce biomolecule readily available for biological investigations and provided confirmation of its structural assignment. However, the developed route was not without drawbacks. For example, the synthesis of β-siloxyaldehyde fragment **14** required careful handling of the labile β,γ-unsaturated aldehyde **17**, prior synthesis of the (*R*)-NOBIN catalyst (four steps from rather expensive commercially available reagents[33,37]), and the potentially pyrophoric palladium catalyst for hydrogenation, all of which hampered its application on gram-scale synthesis. To overcome these limitations, and with the expectation that development of multiple synthetic routes toward Δ^{12}-PGJ$_3$ (**1**) would allow more facile modification of the parent structure, we set out to develop alternative strategies toward the two key fragments **13** and **14**. Below, we describe our second- and third-generation syntheses of β-siloxyaldehyde fragment **14** featuring conceptually different means to construct the C15 hydroxyl-bearing stereocenter.

The second-generation retrosynthetic analysis of aldehyde **14** stemmed from its discernible structural relationship with alcohol **43** (Figure 6), a known compound that could be prepared in enantioenriched form by a catalytic asymmetric Keck allylation between aldehyde **44** and allyl tri-*n*-butylstannane (**45**).[38] Conversion of **43** to **14** was anticipated to be straightforward through successive functional group manipulations at both ends of the starting material (**43**). Thus, in the forward sense (Scheme 4), exposure of aldehyde **44** and stannane **45** to catalytic amounts of Ti(O*i*Pr)$_4$ and (*S*)-BINOL in the presence of oven-dried (100 °C) 4 Å molecular sieves (4 Å MS) afforded homoallylic alcohol **43** in 87% yield and >95% *ee*.[38,39] It has been suggested by Kurosu and Lorca that 4 Å MS actually serve as a controllable water source in Ti(O*i*Pr)$_4$/BINOL-catalyzed Keck allylation reactions.[39] In line with this notion, we found in our case that repetitive heating of the molecular sieves with a propane flame under high vacuum led to significantly decreased substrate conversion. When the oven-dried

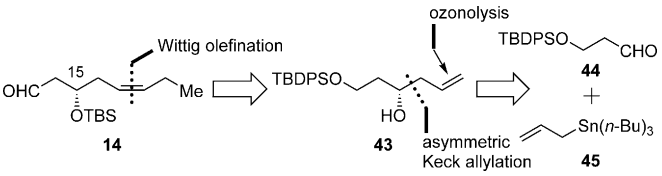
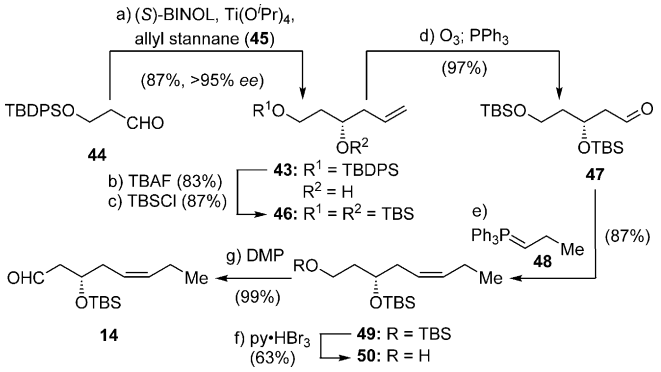


Figure 6. Second-generation retrosynthetic analysis of aldehyde fragment **14**. TBDPS = *tert*-butyldiphenylsilyl.



Scheme 4. Second-generation synthesis of aldehyde fragment **14** via asymmetric Keck allylation. Reagents and conditions: a) Ti(O*i*Pr)$_4$ (0.025 equiv), (*S*)-BINOL (0.05 equiv), 4 Å MS, toluene, 25 °C, 2.5 h; then **44** (1.0 equiv), CH_2=$CHCH_2Sn(n$Bu$)_3$ (**45**, 1.5 equiv), −78 to −20 °C, 5 d, 87%; b) TBAF (2.0 equiv), THF, 25 °C, 2 h, 83%; c) TBSCl (2.5 equiv), imid. (5.0 equiv), CH_2Cl_2, 25 °C, 15 h, 87%; d) O_3, $NaHCO_3$, CH_2Cl_2, −78 °C; then PPh_3 (2.0 equiv), 25 °C, 3 h, 97%; e) $BrPh_3P(CH_2)_2Me$ (2.0 equiv), NaHMDS (2.0 equiv), THF, −78 to 25 °C, 2 h, 87%; f) py·HBr_3 (0.1 equiv), MeOH, −10 °C, 1.25 h, 63%; g) DMP (1.3 equiv), CH_2Cl_2, 0 to 25 °C, 2 h, 99%. BINOL = 1,1′-binaphthol; py = pyridine.

4 Å MS were used directly, consistent yields and enantioselectivities could be obtained on gram-scale.

Deprotection of the TBDPS group in **43** (TBAF, 83%, Scheme 4) and protection of the resulting diol (TBSCl, imid., 87%) afforded bis-TBS ether **46**, whose ozonolysis (O_3; PPh_3, 97%)[40] and Wittig olefination [$BrPh_3P(CH_2)_2$-Me, NaHMDS, 87%] gave (*Z*)-alkene **49** as the major geometrical isomer [(*Z*):(*E*) ca. 8:1]. Selective desilylation of **49** was carried out with catalytic amounts of py·HBr_3 in MeOH.[41] Although the yield of primary alcohol **50** was moderate (63%) and attempts to improve the selectivity by using a bulkier alcohol nucleophile (e.g., *i*PrOH)[42] were unsuccessful, the over-desilylated diol byproduct (not shown) could be recycled by converting it back to bis-TBS ether **49**. Finally, oxidation of alcohol **50** with DMP provided the β-siloxyaldehyde fragment **14** in excellent yield (99%).

One shortcoming of the above strategy was the use of the toxic stannane reagent **45** (Scheme 4). To circumvent this problem, we turned our focus to a chiral-pool-based strategy. Specifically, we postulated that the known terminal epoxide **51**,[43] available in three steps from L-aspartic acid (**52**), could serve as a suitable precursor to aldehyde **14** as shown in retrosynthetic format in Figure 7. Scheme 5 summarizes the preparation of aldehyde fragment **14** starting from L-aspartic acid (**52**). BF_3·Et_2O-mediated epoxide opening of **51** with the lithium acetylide derived from 1-butyne and *n*-butyllithium provided, after silylation of the newly generated homopropargylic alcohol **53**, internal alkyne **54** (80% over the two steps). Hydrogenation of the latter with Lindlar catalyst gave small amounts of the undesired (*E*)-isomer [(*Z*):(*E*) ca. 20:1]. On the other hand, P-2 nickel boride, generated from $Ni(OAc)_2$·$4H_2O$, $NaBH_4$ and 1,2-ethylenediamine,[44] gave the desired (*Z*)-alkene in high yield (93%) and higher (*Z*):(*E*) selectivity (ca. 30:1). The synthesis of

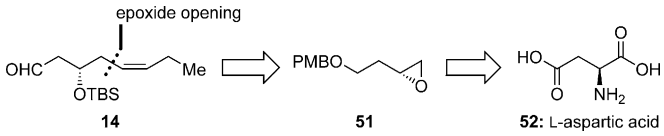
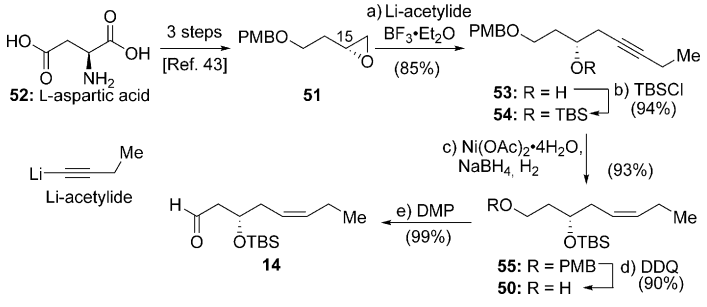


Figure 7. Third-generation retrosynthetic analysis of aldehyde fragment **14**.



Scheme 5. Third-generation synthesis of aldehyde fragment **14** from L-aspartic acid (**55**). Reagents and conditions: a) 1-butyne (2.0 equiv), *n*BuLi (1.5 equiv); then **51** (1.0 equiv), BF_3·Et_2O (1.4 equiv), THF, −78 °C, 2 h, 85%; b) TBSCl (1.5 equiv), imid. (3.0 equiv), CH_2Cl_2, 0 to 25 °C, 4 h, 94%; c) $Ni(OAc)_2$·$4H_2O$ (0.16 equiv), $NaBH_4$ (0.38 equiv), 1,2-ethylenediamine (1.8 equiv), H_2, EtOH, 25 °C, 6 h, 93%; d) DDQ (1.5 equiv), CH_2Cl_2/pH 7 buffer (20:1), 0 °C, 12 h, 90%; e) DMP (1.5 equiv), CH_2Cl_2, 0 to 25 °C, 2 h, 99%.

the β-siloxyaldehyde fragment **14** was then completed upon PMB-deprotection of the olefin (DDQ, 90%) and subsequent oxidation of the resulting primary alcohol (**50**, DMP, 99%).

The above second- and third-generation approaches to aldehyde **14** greatly improved the scalability of this key building block by avoiding the use of sensitive intermediates or expensive catalyst precursors. As a demonstration of the efficiency of our synthesis, we note that 25 grams of alcohol **50** (Scheme 5, the direct precursor of aldehyde **14**) could be prepared in a single batch from commercially available L-aspartic acid (**52**) following this third-generation synthetic route (Scheme 5).

Improved syntheses of cyclopentenone fragment 13

Concurrent with the above efforts, we were also searching for alternative syntheses of the cyclopentenone fragment **13** (Figure 4), with the ultimate goal of devising a short, enantioselective and readily scalable synthesis of this 4-alkyl-substituted 2-cyclopentenone, a commonly found structural motif in natural and designed molecules of biological and medical importance.[13,45–47] Furthermore, such molecules often serve as building blocks or intermediates in the construction of target molecules.[48,49] Not surprisingly, enantioselective synthesis of 4-substituted 2-cyclopentenones has been the subject of numerous studies, with notable successes achieved through enzymatic resolution,[50] Pauson–Khand reaction,[51] Nazarov cyclization,[52] and asymmetric Tsuji–Trost allylation as utilized in our original synthesis of this fragment (see Scheme 1).

The basic concept of our second-generation strategy toward cyclopentenone fragment **13**, or more specifically to its viable precursor **21** is shown retrosynthetically in Figure 8. Thus, it was envisioned that **21** could be formed from bridged lactone **57** whose origin was traced to bicyclic ketone **56** via a Baeyer–Villiger reaction. The inspiration and confidence in this plan came from Corey's landmark synthesis of $PGF_{2\alpha}$ (**61**, Figure 8b), in which substituted bicyclic ketone **59** was converted to lactone **60** with *m*-CPBA in high yield, and thence to $PGF_{2\alpha}$ as indicated in Figure 8b.[53] This seemingly straightforward route (Figure 8a) suffered in reality from a severe flaw (vide infra), which was, interestingly but perhaps fortunately in retrospect, overlooked before attempting its laboratory execution.

Bicyclic ketone **56** was prepared following a modified literature procedure as shown in Scheme 6a.[54] Thus, enantioselective hydrosilylation of norbornadiene (**62**) with $HSiCl_3$ in the presence of catalytic amounts of [(η^3-C_3H_5)$PdCl]_2$ and (*S*)-MOP afforded a crude silane **62a**, which was subjected to a sequential Tamao–Fleming reaction (KF, H_2O_2, 50% from **62**) and Swern oxidation [$(COCl)_2$, DMSO, 90%] to give ketone **56** in enantioenriched form.[54,55] We note that the hydrosilylation step was amenable to large-scale reactions due to the exceedingly low catalyst loading (0.05 mol%) and solvent-free conditions. Exposure of ketone **56** to several standard Baeyer–Villiger oxidation conditions (e.g., *m*-CPBA, H_2O_2/NaOH) resulted in the predominant formation of rearranged lactone **58**,

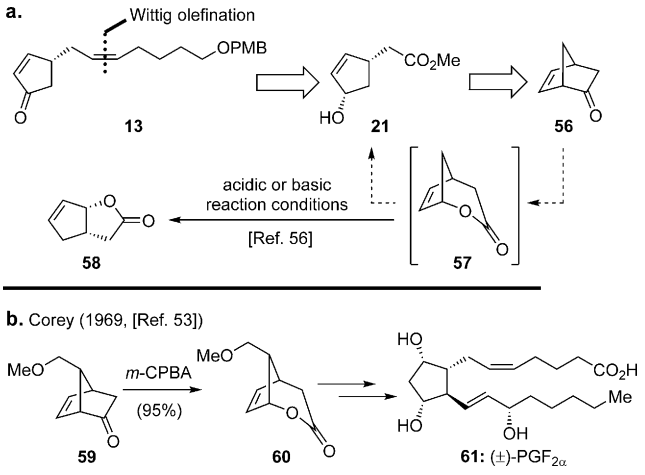
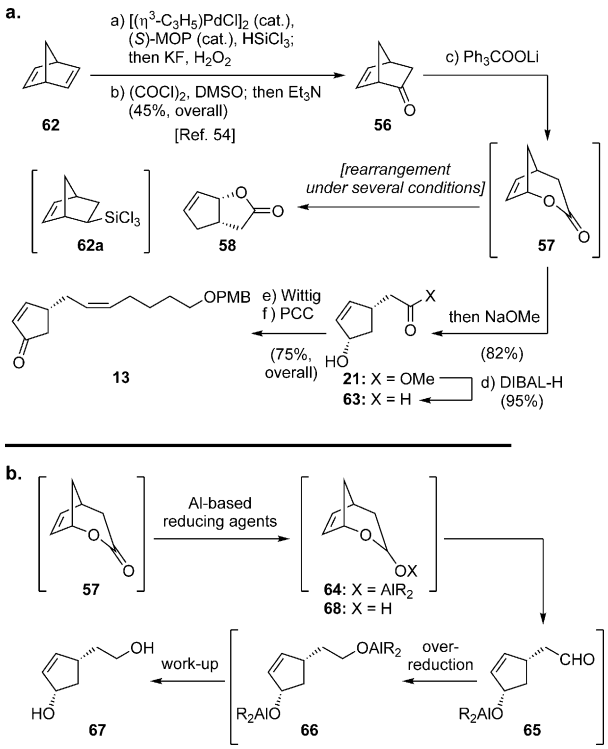


Figure 8. Second-generation retrosynthetic analysis of cyclopentenone fragment **13**.



Scheme 6. Second-generation synthesis of cyclopentenone fragment **13** via Baeyer–Villiger oxidation. Reagents and conditions: a) $HSiCl_3$ (0.99 equiv), $[(\eta^3\text{-}C_3H_5)PdCl]_2$ (0.0005 equiv), (*S*)-MOP (0.002 equiv), neat, −10 to 0 °C, 24 h; then KF (6.0 equiv), $KHCO_3$ (9.0 equiv), H_2O_2 (35% aq., 6.2 equiv), THF/MeOH (1:1), 25 °C, 12 h, 50%; b) $(COCl)_2$ (1.3 equiv), DMSO (1.4 equiv), CH_2Cl_2, −78 °C, 30 min; then Et_3N (2.8 equiv), −78 to 25 °C, 2 h, 90%; c) Ph_3COOH (1.3 equiv), *n*BuLi (1.2 equiv), −78 °C, 6 h; then NaOMe (2.0 equiv), 0 °C, 4 h, 82%; d) DIBAL-H (2.2 equiv), CH_2Cl_2, −78 °C, 45 min, 95%; e) $IPh_3P(CH_2)_5OPMB$ (**26**, 2.5 equiv), NaHMDS (3.0 equiv), THF, −78 to 25 °C, 18 h; f) PCC (2.0 equiv), CH_2Cl_2, 25 °C, 3 h, 73% for the two steps. DMSO = dimethyl sulfoxide; MOP = 2-(diphenylphosphino)-2′-methoxy-1,1′-binaphthol.

along with small amounts of the desired product **57** (Scheme 6a) and the corresponding ring-opened hydroxyl carboxylic acids (not shown). Literature survey revealed numerous reports on the notorious proclivity of lactone **57** to isomerize to **58** under both acidic and basic reaction conditions, owing to its inherent strain and the allylic nature of the carboxylate functionality.[56] This behavior largely explains the obscurity of lactone **57** as a useful chiral synthon, despite its initial identification as early as 1958.[56a]

Although dismayed by this finding, we were tempted by the conciseness of the proposed synthesis of fragment **13** (Figure 8) and decided to address this problem. However, none of the common tactics, including buffering the acidic conditions (e.g., *m*-CPBA/$NaHCO_3$), reducing the strength of base (e.g., H_2O_2 with $NaHCO_3$ or Na_2HPO_4 instead of NaOH) or changing of peroxide reagent (e.g., *t*BuOOH) proved effective. Eventually, we were delighted to discover that Ph_3COOLi (generated in situ from Ph_3COOH and *n*BuLi at −78 °C, Scheme 6a)[57] was exceptionally effective, furnishing the desired lactone **57** with complete substrate conversion and minimal isomerization (as judged by TLC monitoring of the reaction mixture). While attempts to isolate this coveted intermediate (i.e., **57**) failed, direct addition of NaOMe (as MeOH solution) to the reaction mixture followed by warming to 0 °C provided the ring-opened methyl ester **21** in 82% yield. Following our previously developed sequence (see Scheme 1), reduction of ester **21** to the corresponding aldehyde (**63**) (DIBAL-H, 95%) followed by Wittig olefination [$IPh_3P(CH_2)_5OPMB$, NaHMDS] and oxidation (PCC, 73% for the two steps) completed the synthesis of enone **13** in six total steps (cf. nine steps for the original route, Scheme 1). Interestingly, attempted direct reduction of the crude lactone **57** to aldehyde **63** with several Al-based reagents (e.g., DIBAL-H, Red-Al, $iBu_2AlH{\cdot}KOtBu$[58]) invariably led to a mixture of **63** and diol **67**,[59] even with only one equivalent of the reducing agent (see Scheme 6b). We hypothesize that the strained nature of the expected "tetrahedral intermediate" (**64**, Scheme 6b) caused it to break down to aldehyde **65** even at the low temperature of the reaction. The latter was then further reduced under the reaction conditions to afford diol **67** after aqueous work-up. In accord with this hypothesis, the ^1H NMR spectrum of aldehyde **63** showed no detectable signals of the corresponding bridged hemiacetal **68** (the speculative hydrolysis product of intermediate **64**, Scheme 6b), indicating the predominant existence of the open-chain tautomer of this species.

Aiming for further improvement, and in search of an alternative mode of attachment of the top side-chain, and in order to further shorten the synthetic route toward cyclopentenone fragment **13**, we opted for the Stork–Danheiser enone synthesis[60] (Figure 9), with the hope that a suitable chiral auxiliary

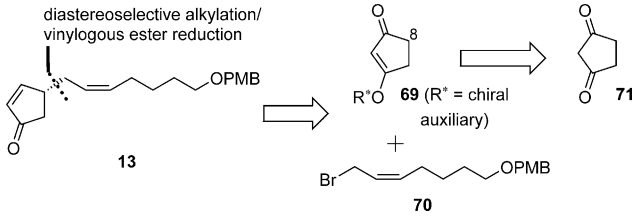
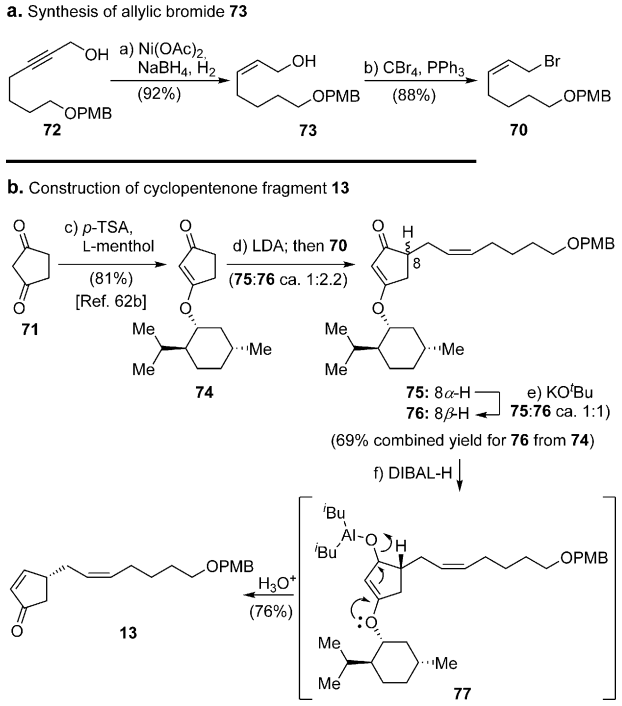


Figure 9. Third-generation retrosynthetic analysis of cyclopentenone fragment **13**.

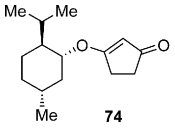
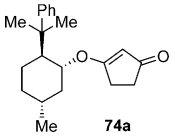
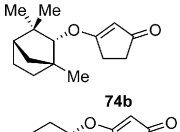
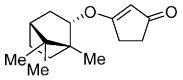
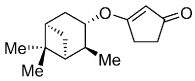
(e.g., L-menthol) incorporated into the vinylogous ester **69** would exert a degree of stereoinduction on the enolate alkylation at C8 (PGJ numbering) with allylic bromide **70**. Should the diastereoselectivity be moderate, the two diastereomeric alkylation products were expected to be separable by chromatography, and the undesired diastereomer potentially could be isomerized under basic conditions. If successful, this route toward enone **13** would only include three steps from commercially available 1,3-cyclopentanedione (**71**), namely auxiliary incorporation, diastereoselective alkylation, and vinylogous ester reduction (see Figure 9).

Execution of this plan began with the preparation of allylic bromide **70** as outlined in Scheme 7a. Thus, (*Z*)-selective partial hydrogenation of the internal alkyne in **72**[61] proceeded smoothly with 1,2-ethylenediamine-modified nickel boride[44] and H_2 (1 atm) in the absence of light to generate allylic alcohol **73** (92%), which was then converted to the desired allylic bromide **70** (CBr_4, PPh_3, 88%). On the other hand, installation of the L-(−)-menthol auxiliary, which had been successfully applied in related transformations,[62] was achieved by acid-catalyzed formation of vinylogous ester **74**[62b] (Scheme 7b), setting the stage for the diastereoselective alkylation. In the event, regioselective deprotonation of **74** with LDA in the presence of DMI (as an eco-friendly surrogate for HMPA), followed by addition of allylic bromide **73** furnished a mixture of C8-epimers **75** and **76**, with the major product being the desired diastereomer **76** (**75**:**76** ca. 1:2.2, Scheme 7b). As expected, the two diastereomers could be readily separated by flash column chromatography, and the undesired isomer **75** could be partially epimerized by exposure to KO*t*Bu/*t*BuOH[62a] (**75**:**76** ca. 1:1). This sequence was successfully carried out on a relatively large scale providing over ten grams of vinylogous ester **76** (69% combined yield from **74**). The menthol auxiliary was then reductively cleaved from **76** with DIBAL-H to afford enone **13** (76%) via the intermediacy of aluminum complex **77** (Scheme 7b). It should be noted that among the several chiral substrates we screened [i.e., those derived from (−)-menthol (**74**), (−)-8-phenylmenthol (**74a**), (+)-fenchol (**74b**), (+)-borneol (**74c**) and (+)-isopinocampheol (**74d**), see Table 2], (−)-8-phenylmenthol and (+)-fenchol (entries 2 and 3, Table 2, respectively) gave comparable results. However, (−)-menthol was preferred due to its lower cost.



Scheme 7. Third-generation synthesis of cyclopentenone fragment **13** via diastereoselective alkylation. Reagents and conditions: a) $Ni(OAc)_2{\cdot}4H_2O$ (0.16 equiv), $NaBH_4$ (0.38 equiv), 1,2-ethylenediamine (1.8 equiv), H_2, EtOH, 25 °C, 6 h, 92%; b) CBr_4 (1.6 equiv), PPh_3 (1.6 equiv), MeCN, −10 °C, 30 min, 88%; c) *p*-TSA·H_2O (0.1 equiv), L-(−)-menthol (1.2 equiv), C_6H_6, 80 °C, 8 h, 81%; d) LDA (1.10 equiv), DMI (1.2 equiv), THF, −78 °C, 45 min; then **70** (1.2 equiv), −40 °C, 8 h (**75**:**76** ca. 1:2.2); then chromatographic separation; e) KO*t*Bu (0.5 equiv), *t*BuOH (0.6 equiv), THF, 0 °C, 2 h (**75**:**76** ca. 1:1); then chromatographic separation, 69% combined yield of **76** for the two steps; f) DIBAL-H (1.5 equiv), Et_2O, 0 °C, 30 min, 76%. *p*-TSA = *para*-toluenesulfonic acid.

Table 2. Optimization of diastereoselective alkylation of cyclopentenones.[a]

Entry	Substrate	Yield [%][b]	d.r.
1	 **74**	79	69:31[c]
2	 **74a**	79	69:31[c]
3	 **74b**	87	65:35[c]
4	 **74c**	50	54:46[c]
5	 **74d**	57	59:41[c]

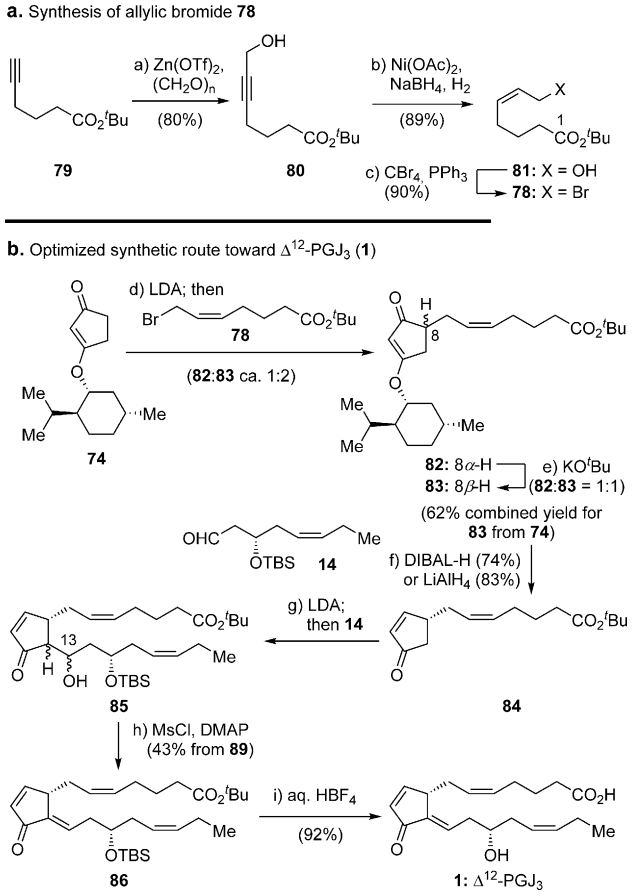
[a] Reactions were carried out on 1.0 mmol scale at 25 °C. Reagents and conditions: LDA (1.15 equiv), DMI (1.2 equiv), THF, −78 °C; then **70** (1.3 equiv), −40 °C, 8 h. [b] Yields refer to chromatographically isolated and spectroscopically pure products. [c] relative stereochemistry d.r.

Streamlined synthesis of Δ^{12}-PGJ_3 (1)

With the syntheses of both key fragments **13** and **14** optimized, their union and subsequent conversion to Δ^{12}-PGJ_3 (**1**) could follow the previously developed sequence (see Scheme 3a). However, careful inspection of the final stage of the original synthesis revealed further room for improvement. Specifically, the PMB-protected C1 primary alcohol **39** (see Scheme 3a) was transformed to the natural product (i.e., **1**)

through four steps, namely PMB-deprotection, oxidation to the aldehyde, subsequent oxidation to the carboxylic acid, and eventual TBS-removal with aqueous HF. We reasoned that if the C1 *tert*-butyl ester counterpart of **39** (i.e., **86**, Scheme 8b) could be prepared, subjection of this intermediate to the action of suitable acidic conditions should cleave both the TBS group and the *tert*-butyl ester, thereby shortening the entire synthesis by three steps.

To implement this strategy, we began by targeting allylic bromide **78** (Scheme 8a) bearing a *tert*-butyl ester group at C1. Starting from the readily available terminal alkyne **79**[63] (Scheme 8a), the synthesis of propargylic alcohol **80** was accomplished by using the conditions developed by Hale et al. [$Zn(OTf)_2$, TMEDA, $(CH_2O)_n$, 80%].[64] Adapted from Carreira's asymmetric alkynylation conditions,[65] this protocol for hydroxymethylation of terminal alkynes avoids the use of *n*BuLi, proceeding instead via the corresponding alkynylzinc triflate. Partial hydrogenation of the alkyne moiety in **80** [H_2, $Ni(OAc)_2 \cdot 4H_2O$, $NaBH_4$, 1,2-ethylenediamine, 89%][44] and conversion of the resulting primary alcohol **81** to allylic bromide **78** (CBr_4, PPh_3, 90%) followed previously developed conditions as described in Scheme 7a for the preparation of its C1-OPMB counterpart (i.e., **70**).



Scheme 8. Streamlined synthesis of Δ^{12}-PGJ_3 (**1**). Reagents and conditions: a) $Zn(OTf)_2$ (1.9 equiv), TMEDA (2.0 equiv), Et_3N (2.0 equiv), $(CH_2O)_n$ (5.0 equiv), toluene, 25 °C, 48 h, 80%; b) $Ni(OAc)_2 \cdot 4H_2O$ (0.16 equiv), $NaBH_4$ (0.38 equiv), 1,2-ethylenediamine (1.8 equiv), H_2, EtOH, 25 °C, 8 h, 89%, (*Z*):(*E*) = 50:1; c) CBr_4 (1.5 equiv), PPh_3 (1.5 equiv), MeCN, 0 °C, 30 min, 90%; d) LDA (1.10 equiv), THF, −78 °C; then **74** (1.0 equiv), −78 °C, 45 min; then **78** (1.2 equiv), DMI (1.2 equiv), −78 to 0 °C, 6 h (**82**:**83** ca. 1:2); then chromatographic separation; e) KO*t*Bu (0.5 equiv), *t*BuOH (0.6 equiv), THF, 0 °C, 45 min (**82**:**83** ca. 1:1); then chromatographic separation, 62% combined yield of **83** for the two steps; f) DIBAL-H (2.0 equiv), Et_2O, −40 °C, 1 h, 74%; or $LiAlH_4$ (0.6 equiv), THF, −40 °C, 1 h, 83%; g) **84** (1.0 equiv), **14** (1.3 equiv), premixing, THF, −78 °C; then LDA [2.0 equiv (dropwise over 1 h)], −78 °C; then −78 °C, 30 min; h) MsCl (3.0 equiv), DMAP (15 equiv), CH_2Cl_2, −10 to 25 °C, 12 h, 43% for the two steps (49% based on recovered **84**); i) HBF_4 (48% aq., 25 equiv), solvent, 0 °C, 30 min, 92%. TMEDA = *N*,*N*,*N*′,*N*′-tetramethylethylenediamine.

As outlined in Scheme 8b, alkylation of vinylogous ester **74** (prepared according to Scheme 7b) with allylic bromide **78** gave a mixture of separable diastereomers **82** and **83** (**82**:**83** ca. 1:2). The minor, undesired diastereomer **82** was subjected to KO*t*Bu/*t*BuOH epimerization to obtain an equal mixture of **82** and **83**, thereby providing **83** in 62% combined yield from **74**. Reduction of vinylogous ester **83** with DIBAL-H at 0 °C was initially troublesome due to concomitant reduction of the *tert*-butyl ester moiety. However, good yield of enone **84** (74%) was restored by lowering the reaction temperature to −40 °C. Switching the reducing agent to $LiAlH_4$ further improved the yield of this reduction to 83%. This optimized sequence allowed the preparation of enone **84** on gram scale, setting the stage for its union with the aldehyde fragment **14**.

As it turned out, the presence of the ester moiety in **84** demanded a reevaluation of the aldol reaction, as the originally employed conditions (addition of enone **84** to LDA, followed by addition of aldehyde **14**) provided a significant amount of bis-aldol product as a result of deprotonation at the α-positions of both the ketone and the ester moieties, respectively. On the other hand, when LDA was added dropwise to a solution of **84** at −78 °C, the resulting enolate was trapped by the remaining enone itself before the addition of aldehyde **14**. We reasoned that such enone dimerization process could be inhibited by addition of LDA to a pre-mixed solution of **84** and **14** at −78 °C. In practice, this protocol successfully delivered the coveted aldol product **85** with markedly improved efficiency, despite the potential competing deprotonation of the α-H of the aldehyde (**14**). This remarkable chemoselectivity (selective enolate generation from a ketone in the presence of an aldehyde) may be attributed in part to the bulky β-siloxy group of the aldehyde fragment, which blocked access of LDA to the α-H. Proceeding with the streamlined synthesis, it was discovered that the original, two-step protocol for elimination (MsCl, Et_3N; Al_2O_3) could now be accomplished in one step by treating aldol product **85** with MsCl in the presence of excess DMAP, providing the cross-conjugated dienone **86** in 43% yield (49% based on recovered enone **84**). Finally, we were pleased to find that both the *tert*-butyl and the TBS groups were readily cleaved under the influence of 48% aqueous HBF_4 (92%), thus completing the total synthesis of Δ^{12}-PGJ_3 (**1**) in six steps from commercially available 1,3-cyclopentanedione (**74**) (cf. 16 steps for the first-generation synthesis).

Conclusion

The total synthesis of Δ^{12}-PGJ_3 (**1**) was accomplished through a number of different synthetic routes that evolved from our

original strategy of 16 steps to a streamlined process consisting of only six steps from commercially available starting materials. Highlights of the described work include a catalytic asymmetric Tsuji–Trost coupling reaction, a catalytic asymmetric Mukaiyama aldol reaction, a Rh-catalyzed C–H functionalization, preparation and utilization of the chiral version of a bicyclic lactone building block for the synthesis of substituted cyclopentenones, and a diastereoselective alkylation of cyclopentenones carrying chiral menthol-type auxiliaries. The developed synthetic routes are suited for the synthesis of a wide range of analogues of Δ^{12}-PGJ$_3$ (**1**) and related compounds, as well as large scale preparation of Δ^{12}-PGJ$_3$. Applications of these synthetic strategies and technologies to the synthesis of designed analogues of this class of compounds as potential anticancer agents are described in reference [66].

Experimental Section

For full experimental procedures and physical properties of compounds see Supporting Information (S1–S127).

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Keywords: antitumor agent · asymmetric catalysis · chiral auxiliary · prostaglandin · total synthesis

[1] S. A. Williams, W. C. Anderson, M. T. Santaguida, S. J. Dylla, *Lab. Invest.* **2013**, *93*, 970–982.
[2] For reviews on CSCs, see: a) L. Han, S. Shi, T. Gong, Z. Zhang, X. Sun, *Acta Pharm. Sin. B* **2013**, *3*, 65–75; b) P. A. Sotiropoulou, M. S. Christodoulou, A. Silvani, C. Herold-Mende, D. Passarella, *Drug Discovery Today* **2014**, *19*, 1547–1562; c) H. Qiu, X. Fang, Q. Luo, G. Ouyang, *Cell. Mol. Life Sci.* **2015**, *72*, 3411–3424.
[3] a) S. Hegde, N. Kaushal, K. C. Ravindra, C. Chiaro, K. T. Hafer, U. H. Gandhi, J. T. Thompson, J. P. van den Heuvel, M. J. Kennett, P. Hankey, R. F. Paulson, K. S. Prabhu, *Blood* **2011**, *118*, 6909–6919; b) K. S. Prabhu, R. F. Paulson, S. Hegde, N. Kaushal, U. H. Gandhi, WO 2013/003729A1, January 3, 2013.
[4] A. K. Kudva, N. Kaushal, S. Mohinta, M. J. Kennett, A. August, R. F. Paulson, K. S. Prabhu, *PLOS One* **2013**, *8*, e80622/1–e80622/10.
[5] A. Sinclair, A. L. Latif, T. L. Holyoake, *Br. J. Pharmacol.* **2013**, *169*, 1693–1707.
[6] a) F. A. Fitzpatrick, M. A. Wynalda, *J. Biol. Chem.* **1983**, *258*, 11713–11718; b) T. Shibata, M. Kondo, T. Osawa, N. Shibata, M. Kobayashi, K. Uchida, *J. Biol. Chem.* **2002**, *277*, 10459–10466.
[7] J. Lefils-Lacourtablaise, M. Socorro, A. Géloën, P. Daira, C. Debard, E. Loizon, M. Guichardant, Z. Dominguez, H. Vidal, M. Lagarde, N. Bernoud-Hubac, *PLOS One* **2013**, *8*, e63997/1–e/63997/12.
[8] S. Sugiura, T. Toru, T. Tanaka, A. Hazato, N. Okamura, K. Bannai, K. Manabe, S. Kurozumi, R. Noyori, *Chem. Pharm. Bull.* **1984**, *32*, 4658–4661.
[9] H. Sasaki, S. Niimi, M. Akiyama, T. Tanaka, A. Hazato, S. Kurozumi, S. Fukushima, M. Fukushima, *Cancer Res.* **1999**, *59*, 3919–3922.
[10] K. Iguchi, S. Kaneta, K. Mori, Y. Yamada, A. Honda, Y. Mori, *Tetrahedron Lett.* **1985**, *26*, 5787–5790.
[11] S. M. Verbitski, J. E. Mullally, F. A. Fitzpatrick, C. M. Ireland, *J. Med. Chem.* **2004**, *47*, 2062–2070.
[12] M. Suzuki, M. Mori, T. Niwa, R. Hirata, K. Furuta, T. Ishikawa, R. Noyori, *J. Am. Chem. Soc.* **1997**, *119*, 2376–2385.
[13] S. Das, S. Chandrasekhar, J. S. Yadav, R. Grée, *Chem. Rev.* **2007**, *107*, 3286–3337, and references therein.
[14] E. J. Corey, C. J. Helal, *Angew. Chem. Int. Ed.* **1998**, *37*, 1986–2012; *Angew. Chem.* **1998**, *110*, 2092–2118.
[15] a) H. B. Kagan, O. Riant, *Chem. Rev.* **1992**, *92*, 1007–1019; b) E. J. Corey, *Angew. Chem. Int. Ed.* **2002**, *41*, 1650–1667; *Angew. Chem.* **2002**, *114*, 1724–1741.
[16] K. C. Nicolaou, P. Heretsch, A. ElMarrouni, C. R. H. Hale, K. K. Pulukuri, A. K. Kudva, V. Narayan, K. S. Prabhu, *Angew. Chem. Int. Ed.* **2014**, *53*, 10443–10447; *Angew. Chem.* **2014**, *126*, 10611–10615.
[17] For previous syntheses on "J-series" cross-conjugated dienone prostaglandins, see: a) J. F. Bickley, V. Jadhav, S. M. Roberts, M. G. Santoro, A. Steiner, P. W. Sutton, *Synlett* **2003**, 1170–1174; b) K. M. Brummond, P. C. Sill, H. Chen, *Org. Lett.* **2004**, *6*, 149–152; c) M. Iqbal, Y. Li, P. Evans, *Tetrahedron* **2004**, *60*, 2531–2538; d) H. P. Acharya, Y. Kobayashi, *Tetrahedron Lett.* **2004**, *45*, 1199–1202; e) H. P. Acharya, Y. Kobayashi, *Tetrahedron* **2006**, *62*, 3329–3343; f) H. Tanaka, T. Hasegawa, N. Kita, H. Nakahara, T. Shibata, S. Oe, M. Ojika, K. Uchida, T. Takahashi, *Chem. Asian J.* **2006**, *1*, 669–677; g) N.-J. Kim, H. Moon, T. Park, H. Yun, J.-W. Jung, D.-J. Chang, D.-D. Kim, Y.-G. Suh, *J. Org. Chem.* **2010**, *75*, 7458–7460.
[18] a) M. Iqbal, P. Evans, *Tetrahedron Lett.* **2003**, *44*, 5741–5745; b) J. P. Eddolls, M. Iqbal, S. M. Roberts, M. G. Santoro, *Tetrahedron* **2004**, *60*, 2539–2550.
[19] O. Jacquet, T. Bergholz, C. Magnier-Bouvier, M. Mellah, R. Guillot, J.-C. Fiaud, *Tetrahedron* **2010**, *66*, 222–226.
[20] a) B. M. Trost, R. C. Bunt, *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 99–102; *Angew. Chem.* **1996**, *108*, 70–73; b) T. Miyazaki, S. Yokoshima, S. Simizu, H. Osada, H. Tokuyama, T. Fukuyama, *Org. Lett.* **2007**, *9*, 4737–4740.
[21] a) A. J. Catino, R. E. Forslund, M. P. Doyle, *J. Am. Chem. Soc.* **2004**, *126*, 13622–13623. For a review on [Rh$_2$(cap)$_4$]/*t*BuOOH system, see: b) M. O. Ratnikov, M. P. Doyle, *Mendeleev Commun.* **2014**, *24*, 187–196.
[22] N. Chidambaram, S. Chandrasekaran, *J. Org. Chem.* **1987**, *52*, 5048–5051.
[23] P. Marwah, A. Marwah, H. A. Lardy, *Green Chem.* **2004**, *6*, 570–577.
[24] a) T. K. M. Shing, Y.-Y. Yeung, P. L. Su, *Org. Lett.* **2006**, *8*, 3149–3151; b) A. S. Demir, M. Emrullahoglu, *Curr. Org. Synth.* **2007**, *4*, 223–227.
[25] A related olefin transposition was also discovered by Doyle et al. (see ref. [21a]).
[26] K. U. Ingold, *Acc. Chem. Res.* **1969**, *2*, 1–9.
[27] T. Newhouse, P. S. Baran, *Angew. Chem. Int. Ed.* **2011**, *50*, 3362–3374; *Angew. Chem.* **2011**, *123*, 3422–3435, and references therein.
[28] J. J. Luche, *J. Am. Chem. Soc.* **1978**, *100*, 2226–2227.
[29] A. B. Smith III, R. J. Fox, J. A. Vanecko, *Org. Lett.* **2005**, *7*, 3099–3102.
[30] N. Shao, X. Huang, A. Palani, R. Aslanian, A. Buevich, J. Piwinski, R. Huryk, C. Seidel-Dugan, *Synthesis* **2009**, 2855–2872.
[31] L. Wavrin, J. Viala, *Synthesis* **2002**, 326–330.
[32] S. Kiyooka, S. Matsumoto, T. Shibata, K. Shinozaki, *Tetrahedron* **2010**, *66*, 1806–1816.
[33] E. M. Carreira, R. A. Singer, W. Lee, *J. Am. Chem. Soc.* **1994**, *116*, 8837–8838.
[34] T. R. Hoye, C. S. Jeffrey, F. Shao, *Nat. Protoc.* **2007**, *2*, 2451–2458.
[35] The *E*-Δ^{12} geometry was determined based on the chemical shift of the C13-proton: $\delta = 6.60$ ppm; see: a) G. L. Bundy, D. R. Morton, D. C. Peterson, E. E. Nishizawa, W. L. Miller, *J. Med. Chem.* **1983**, *26*, 790–799. For an explanation on this stereochemical convergence, see: b) Y. Kobayashi, M. G. Murugesh, M. Nakano, *Tetrahedron Lett.* **2001**, *42*, 1703–1707.
[36] B. S. Bal, W. E. Childers, Jr., H. W. Pinnick, *Tetrahedron* **1981**, *37*, 2091–2096.
[37] E. Yao, J. Wang, Z. Chen, Y. Ma, *Macromolecules* **2014**, *47*, 8164–8170.
[38] G. E. Keck, D. S. Welch, P. K. Vivian, *Org. Lett.* **2006**, *8*, 3667–3670.
[39] M. Kurosu, M. Lorca, *Synlett* **2005**, 1109–1112.
[40] J. D. White, P. R. Blakemore, C. C. Browder, J. Hong, C. M. Lincoln, P. A. Nagornyy, L. A. Robarge, D. J. Wardrop, *J. Am. Chem. Soc.* **2001**, *123*, 8593–8595.

[41] D. Martinez-Solorio, M. P. Jennings, *Tetrahedron Lett.* **2008**, *49*, 5175 – 5178.
[42] R. Gopinath, B. K. Patel, *Org. Lett.* **2000**, *2*, 4177 – 4180.
[43] a) J. A. Frick, J. B. Klassen, A. Bathe, J. M. Abramson, H. Rapoport, *Synthesis* **1992**, 621 – 623; b) C. W. Wullschleger, J. Gertsch, K.-H. Altmann, *Org. Lett.* **2010**, *12*, 1120 – 1123.
[44] a) H. C. Brown, C. A. Brown, *J. Am. Chem. Soc.* **1963**, *85*, 1005 – 1006; b) C. A. Brown, V. K. Ahuja, *J. Chem. Soc. Chem. Commun.* **1973**, 553 – 554.
[45] a) Y. Ohfune, P. A. Grieco, C. L. J. Wang, G. Majetich, *J. Am. Chem. Soc.* **1978**, *100*, 5946 – 5948; b) P. A. Grieco, Y. Ohfune, G. F. Majetich, C. L. J. Wang, *J. Am. Chem. Soc.* **1982**, *104*, 4233 – 4240.
[46] S.-G. Liao, Z.-J. Zhan, S.-P. Yang, J.-M. Yue, *Org. Lett.* **2005**, *7*, 1379 – 1382.
[47] N. I. Torres, V. Castilla, A. C. Bruttomesso, J. Eiras, L. R. Galagovsky, M. B. Wachsman, *Antiviral Res.* **2012**, *95*, 37 – 48.
[48] a) M. J. Schnermann, L. E. Overman, *J. Am. Chem. Soc.* **2011**, *133*, 16425 – 16427; b) M. J. Schnermann, L. E. Overman, *Angew. Chem. Int. Ed.* **2012**, *51*, 9576 – 9580; *Angew. Chem.* **2012**, *124*, 9714 – 9718.
[49] a) H. Renata, Q. Zhou, P. S. Baran, *Science* **2013**, *339*, 59 – 63; b) H. Renata, Q. Zhou, G. Dünstl, J. Felding, R. R. Merchant, C.-H. Yeh, P. S. Baran, *J. Am. Chem. Soc.* **2015**, *137*, 1330 – 1340.
[50] A. J. H. Klunder, W. B. Huizinga, P. J. M. Sessink, B. Zwanenburg, *Tetrahedron Lett.* **1987**, *28*, 357 – 360.
[51] S. Fonquerna, A. Moyano, M. A. Pericàs, A. Riera, *J. Am. Chem. Soc.* **1997**, *119*, 10225 – 10226.
[52] T. Vaidya, R. Eisenberg, A. J. Frontier, *ChemCatChem* **2011**, *3*, 1531 – 1548, and references therein.
[53] E. J. Corey, N. M. Weinshenker, T. K. Schaaf, W. Huber, *J. Am. Chem. Soc.* **1969**, *91*, 5675 – 5677.
[54] a) Y. Uozumi, S.-Y. Lee, T. Hayashi, *Tetrahedron Lett.* **1992**, *33*, 7185 – 7188; b) P. Ghosh, W. R. Judd, T. Ribelin, J. Aubé, *Org. Lett.* **2009**, *11*, 4140 – 4142.
[55] Enantioselectivity was not determined at this stage. The *er* for downstream intermediate **21** (see Scheme 6) was found to be 94:6 by Mosher ester analysis.
[56] a) J. Meinwald, M. C. Seidel, B. C. Cadoff, *J. Am. Chem. Soc.* **1958**, *80*, 6303 – 6305; b) A. E. Greene, C. Le Drian, P. Crabbé, *J. Am. Chem. Soc.* **1980**, *102*, 7583 – 7584; c) C. Le Drian, A. E. Greene, *J. Am. Chem. Soc.* **1982**, *104*, 5473 – 5483; d) H. Baumgartner, C. Marschner, R. Pucher, H. Grieng, *Tetrahedron Lett.* **1991**, *32*, 611 – 614; e) C. Marschner, J. Baumgartner, H. Griengl, *J. Org. Chem.* **1995**, *60*, 5224 – 5235; f) A.-L. Gustavsson, M. C. Larsson, B. S. Hansson, T. Liljefors, *Bioorg. Med. Chem.* **1997**, *5*, 2173 – 2183. For similar isomerization on related systems, see: g) G. R. Martinez, P. A. Grieco, E. Williams, K. Kanai, C. V. Srinivasan, *J. Am. Chem. Soc.* **1982**, *104*, 1436 – 1438; h) K. Sakai, M. Yamashita, Y. Shibata, *Chem. Lett.* **1986**, *15*, 353 – 356; i) P. Li, J. N. Payette, H. Yamamoto, *J. Am. Chem. Soc.* **2007**, *129*, 9534 – 9535; j) M. Valli, F. Chiesa, A. Gandini, A. Porta, G. Vidari, G. Zanoni, *J. Org. Chem.* **2014**, *79*, 2632 – 2639.
[57] For an example of the use of Ph_3COOH in Baeyer – Villiger oxidation, see: E. J. Corey, M. C. Kang, M. C. Desai, A. K. Ghosh, I. N. Houpis, *J. Am. Chem. Soc.* **1988**, *110*, 649 – 651.
[58] a) M. J. Chae, J. I. Song, D. K. An, *Bull. Korean Chem. Soc.* **2007**, *28*, 2517 – 2518; b) S. J. Choi, K. J. Lee, G. B. Lee, D. K. An, *Bull. Korean Chem. Soc.* **2008**, *29*, 1407 – 1408.
[59] Attempted chemoselective oxidation of the primary alcohol in diol **67** led to a mixture of nonselective oxidation products.
[60] G. Stork, R. L. Danheiser, *J. Org. Chem.* **1973**, *38*, 1775 – 1776.
[61] A. S. Kende, J. I. Martin Hernando, J. B. J. Milbank, *Tetrahedron* **2002**, *58*, 61 – 74.
[62] a) G. B. Dudley, K. S. Takaki, D. D. Cha, R. L. Danheiser, *Org. Lett.* **2000**, *2*, 3407 – 3410; b) S. Iimura, L. E. Overman, R. Paulini, A. Zakarian, *J. Am. Chem. Soc.* **2006**, *128*, 13095 – 13101.
[63] G. Bartoli, M. Bosco, A. Carlone, R. Dalpozzo, E. Marcantoni, P. Melchiorre, L. Sambri, *Synthesis* **2007**, 3489 – 3496.
[64] K. J. Hale, Z. Xiong, L. Wang, S. Manaviazar, R. Mackle, *Org. Lett.* **2015**, *17*, 198 – 201.
[65] a) D. E. Frantz, R. Fässler, E. M. Carreira, *J. Am. Chem. Soc.* **2000**, *122*, 1806 – 1807; b) N. K. Anand, E. M. Carreira, *J. Am. Chem. Soc.* **2001**, *123*, 9687 – 9688.
[66] K. C. Nicolaou, K. K. Pulukuri, S. Rigol, P. Heretsch, R. Yu, C. I. Grove, C. R. H. Hale, A. ElMarrouni, V. Fetz, M. Brönstrup, *J. Am. Chem. Soc.* **2016**, DOI: 10.1021/jacs.6b02075.

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