Domino Aza-Claisen/Mannich Cyclization Reaction from a Chiral α-Alkoxy Enamine or Sequential Alkylation of an α-Alkoxy Ester Enolate or Nitrile Anion, Followed by an Intramolecular Wittig Reaction: Two (3+2) Annulation Routes to Homochiral 4-Alkyl-4-hydroxy-2-cyclopentenone Synthesis

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A study on the enantioselective synthesis of 4-alkyl-4-hydroxyalkylidene-cyclopentenone prostaglandins is reported. Two (3+2) annulation processes allow the synthesis of homochiral 4-alkyl-4-hydroxy-2-cyclopentenones **4**–**5**, **10**–**11**, and **17**. The first process involves a domino aza-Claisen/Mannich cyclization reaction, resulting from the alkylation of an α-alkoxy-enamine, derived from chiral α-alkoxy aldehydes **1**, **9**, or **16** with 3-iodo-2-(methoxymethoxy)prop-1-ene (**3**) as the acetonyl equivalent. The second process is based on the sequential alkylation of esters **21**, **39**, or nitrile **20** with acetonyl equivalents **3** or **25**, followed by an intramolecular Wittig reaction. As an application, the synthesis of the naturally occurring alkylidene-cyclopentenone prostaglandin clavulone II from the spiro[cyclopentene-furan]one **5** and the formal total synthesis of (+/-)-untenone **19** has been carried out.

Introduction

The cyclopentenone prostaglandin (PG) A and J series demonstrate potent antitumor effects in vitro and in vivo.[1] Marine natural prostanoids with high antiproliferative activities, such as clavulone, have been isolated from the Okinawan soft coral *Clavularia viridis*,[2] and natural halogenated compounds such as chlorovulone[3] and punaglandin IV[4] have been isolated from *Telesto reisi* (Figure 1).

These alkylidene-cyclopentenones have been the focus of intense research because of their involvement in cell growth regulation, cell differentiation,[5] and cellular defenses against viral infection.[6] They modulate the expression of a variety of gene and protein functions.[7]

The cross-conjugated dienone structure plays a major role in the biological activities and the antitumor mechanism involves reversible carrier-mediated transport across the cellular and nuclear membranes, followed by covalent attachment to the nuclear protein.[8]

A new and very interesting mechanism of action has recently been reported in the case of Δ^7-PGA$_1$, involving the suppression of tumor cell growth through induction of the protein cyclin-dependent kinase inhibitor p21 by a p53 independent pathway,[9] associated with its increased association with a cyclin A-cyclin-dependent kinase (cdk) in the form of a ternary complex, as well as a reduction of the level of cyclin E.[10]

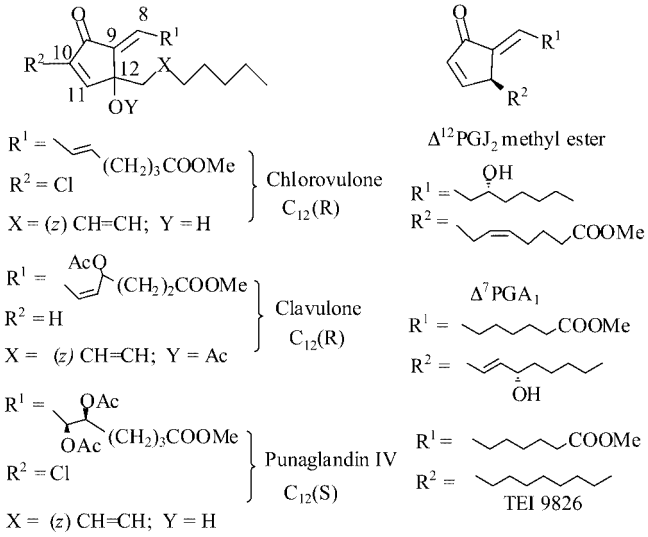

Figure 1. Cyclopentenone prostaglandins

Although many syntheses of naturally occurring PGs have been described,[11] reported SAR studies geared towards obtaining more simplified analogues, particularly more hydrophilic or metabolically more stable ones, have been limited, in spite of the potential therapeutic oppor-

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tunities presented by these compounds.[12] However, the Δ^7-PGA_1 analogue TEI 9826 was recently reported to be an effective agent capable of overcoming cisplatin resistance, and is currently under clinical trial.[13] New biological activities and cellular targets, including anti-inflammatory, anti-neoplastic, and anti-viral activities, have recently been reported.[14] Thus there was a need to develop new methods to elaborate the 4-alkyl-4-hydroxy-2-cyclopentenone framework of these compounds. For these reasons, we initiated a program towards the synthesis of simplified analogues of marine antitumor prostaglandin derivatives of structure **I**.

Results and Discussion

We envisioned the synthesis of these new cyclopentenones **I** (R^1 = halogen, R^2 = H or OH, R^3 = variable chain) through alkylation of chiral 4-alkyl-4-hydroxy cyclopentenone **II** (R^2 = H) or **II′** or (R^2 = OH), potentially synthesizable from spiro-cyclopentenones **III** (for R^2 = H) or **IV** (for R^2 = OH), respectively. These could in turn be elaborated through two different (3 +2) annulation sequences in order to create the quaternary stereogenic center. The first route (A) studied involved a one-pot sequential alkylation of a sugar enamine with an acetonyl equivalent by way of a 3-aza-Claisen reaction (step I), followed by a tandem Mannich reaction resulting in annulation (step II). The second route (B) was based on the alkylation of a cyano- or urono-sugar with the same acetonyl equivalent (step I) followed by an intramolecular Wittig reaction (step II; see Figure 2).

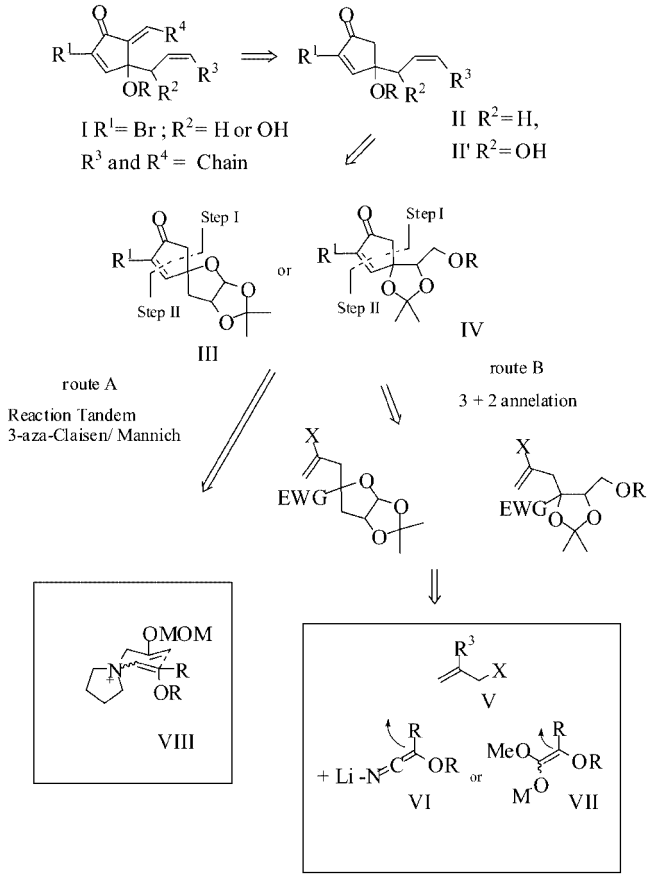
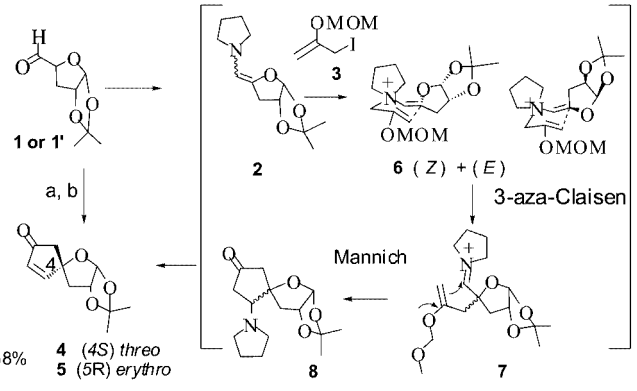


Figure 2. Retrosynthetic analysis

Synthesis of Cyclopentenones Through a 3-Aza-Claisen/ Mannich Tandem Reaction

We first focused on the possible α-allylation of aldehydes **1**[15] or **1′**,[16] easily prepared from diisopropylidene glucose through the use of a 3-aza-Claisen reaction to introduce the allyl moiety,[17] as previously also reported for the synthesis of cyclopentane[18] or cyclopentenone.[19] Thus, treatment of aldehyde **1** with pyrrolidine, according to the conditions described by Secrist III[20] for the C-4 allylation of nucleoside, afforded the pyrrolidino enamine intermediate **2** as a mixture of *Z*/*E* diastereoisomers. The crude **2** obtained after evaporation of the solvent was directly *N*-alkylated at 80 °C in MeCN, with freshly prepared 3-iodo-2-(methoxymethoxy)prop-1-ene (**3**).[21] Surprisingly enough, the product obtained after conventional workup was not the expected C-4 allylated aldehyde resulting from the (3,3)-rearrangement (3-aza-Claisen) but the target cyclopentenones **4** and **5** directly as a mixture of diastereoisomers, thus obtained in 40% yield but in one-pot fashion from aldehydes **1** or **1′** by a domino reaction (Scheme 1).

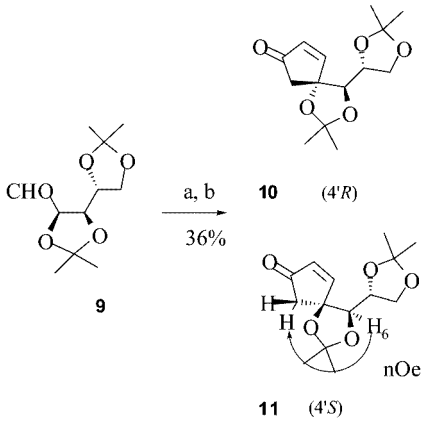


Scheme 1. Reagents and conditions: (a) pyrrolidine, MeCN, 80 °C; (b) CH_2=CH(MOM)−CH_2I (**3**), toluene

The postulated mechanism for this new reaction is depicted in Scheme 1. It involves *N*-alkylation of the *E*/*Z* enamines **2**, giving access to the iminium **6** through an aza-Claisen rearrangement, accelerated by the charged ammonium moiety and, possibly, by the rate-enhancing *p*-donor effect of the vinyl oxygen atom (MOM) in the *chair* transition state.[22] The resulting transient iminium ion **7** generated during this reaction was then trapped in a Mannich reaction involving the nucleophilic carbonyl-like component situated at the enol ether function. This produced the spiro[cyclopentane-furan]one **8**, which subsequently underwent β-elimination of the piperidine moiety to afford the spiro diastereomers **4** (4*S*, *threo*) and **5** (4*R*, *erythro*), isolated in 38% yield (2:1 molar ratio).

The modest diastereoselectivity primarily reflects the two stereochemical factors that could govern the stereocontrol:

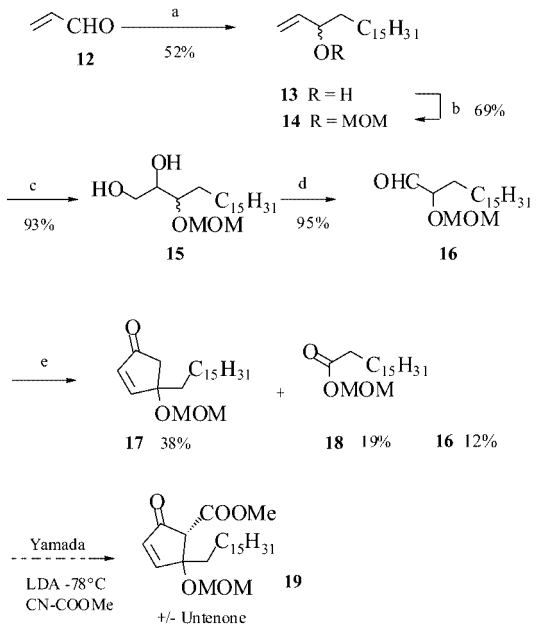
(1) the *Z*/*E* *N*-alkyl olefin geometry determined during enamine formation, and (2) the contribution of the *chair* versus the *boat* transition state (internal asymmetric induction). The sequence of a cationic aza-Claisen rearrangement and a Mannich cyclization to build a pyrrolidine ring has served many research groups as a key step in the total synthesis of alkaloids.[23] The main characteristic feature of this new domino reaction resides in the unusual β-elimination[24] of the pyrrolidine nucleus occurring after the Mannich reaction. The spiro carbon atom configurations in the cyclopentenones **4** and **5** were determined with the aid of NOESY experiments and further confirmed by the RX diagram obtained from the crystalline (4*S*) major compound **4** stereoselectively prepared by the second route (vide infra).[25] We focused on demonstrating the generality of this domino cyclopentannulation with other aldehydes. Thus, the aldehyde **9** − easily obtained from ribose[26] − when treated under the same conditions as described above, gave a 1:1 mixture of two diastereoisomers (4′*R*, **10** and 4′*S*, **11**) in 36% overall yield. The absolute stereochemistry was unambiguously determined by NOESY experiments, since only in the case of the minor *S* isomer was a strong cross-coupling between H-5 and H-6 observed (Scheme 2).



Scheme 2. Reagents and conditions: (a) pyrrolidine, MeCN, 80 °C; (b) CH_2=CH(MOM)−CH_2I (**3**), toluene

Application to the Formal Total Synthesis of (+/-)-Untenone

As another extension of this reaction, a rapid formal total synthesis of natural (+/−)-untenone, a natural cyclopentenone prostaglandin with antiproliferative activity (IC_{50} = 0.4 μg/mL) was carried out, based upon the preparation of the cyclopentenone **17** and its conversion into the target compound according to Yamada.[27] The starting aldehyde was readily obtained as follows. Treatment of acrolein **12** with hexadecylmagnesium bromide at −78 °C to 0 °C in diethyl ether gave the allylic alcohol **13** (52%), which was protected as its *p*-methoxymethyl ether **14**. Oxidation of the double bond to an aldehyde function was achieved in two steps, involving conversion of the alkene into glycol **15** (93%), followed by osmium tetraoxide oxidative cleavage in the presence of lead tetraacetate to give **16** (95% from **15**). Treatment of this under Claisen/Mannich conditions gave the cyclopentenone **17** in 38% yield, together with 12% of recovered starting material **16** and 19% of methoxymethyl ester **18**, probably resulting from the oxidation of the intermediary enamine (Scheme 3).



Scheme 3. Reagents and conditions: (a) $C_{16}H_{33}MgBr$, Et_2O, 0 °C; (b) MOMCl, EtN(*i*Pr)$_2$, CH_2Cl_2, 0 °C (c) OsO_4, NMO acetone/H_2O, 0 °C to room temp.; (d) $[Pb(OAc)_4]$, benzene, 0 °C to room temp.; (e) pyrrolidine, MeCN/toluene, 50 °C then CH_2=CH(MOM)−CH_2I (**3**)

It therefore appears that the original domino 3-aza-Claisen/Mannich reaction is an expeditious method by which to prepare a 4-alkyl-4-hydroxy-2-cyclopentenone directly from an aldehyde. The main drawback of the reaction is in the difficulties that we encountered in controlling the enamine geometry, in the case of a chiral aldehyde. All attempts to improve this diastereoselectivity, in particular by use of calcium hydride − known to produce (*Z*)-enamines preferably − were unsuccessful,[28] as was the use of other additives ($MgBr_2$). In consequence, we decided to focus on a second strategy based on the alkylation of an ester enolate, or nitrile anion, in which facial diastereoselectivity should be much easier to control.

Synthesis of 4-Alkyl-4-hydroxy-2-cyclopentenone by Alkylation of α-Alkoxy Esters and Nitriles

We presumed that alkylation of an α-alkoxynitrile anion **A** or an α-alkoxy ester enolate **B** or **C** should be easily stereocontrolled through the remote stereogenic center present in the heterocycles (the tetrahydrofurans **A** and **B** or the dioxolan ring **C**). The allylated compounds **D** and **E** should later give the spiro 4-hydroxycyclopentenones **F** and **G** by ring closure (Figure 3).

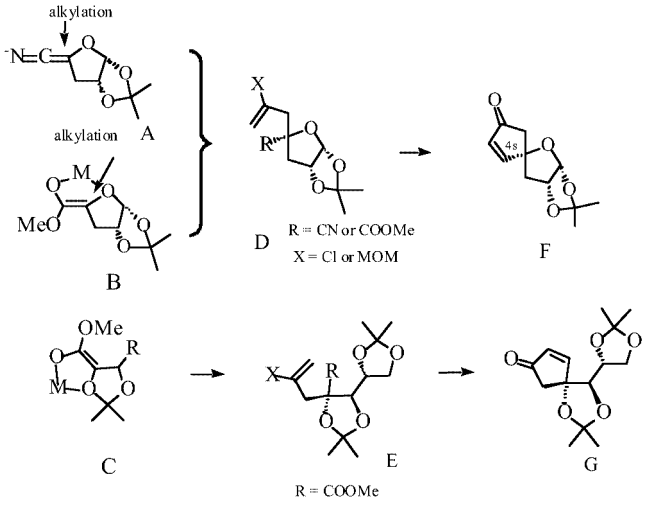
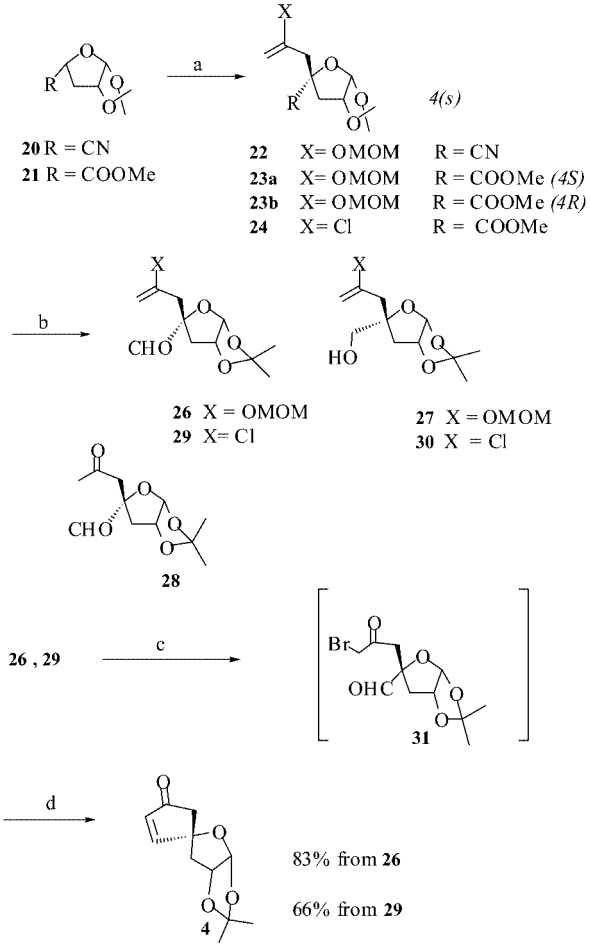


Figure 3. Synthesis of cyclopentenone by alkylation of α-alkoxy esters and nitriles followed by annulation

We first studied the alkylation of the cyano sugar **20** and of the ester **21**, readily prepared from 1,2-*O*-isopropylidene-D-glucose by the procedure of Weidmann et al.[29] For the alkylation, we initially used standard conditions involving deprotonation of the nitrile or of the ester with LDA (1.2 equiv.) at −78 °C for 30 min, followed by addition of the electrophilic 3-iodo-2-(methoxymethoxy)prop-1-ene (**3**). However, the alkylated products **22** and **23a/b** were only obtained in low (15−20%) and irreproducible yields, together with large amounts of starting material. After many experiments,[30] a dramatic increase in the yield was fortunately obtained with the use of KHMDS as the base in an internal quench procedure, as described by Williams et al.[31] and, more recently, by Snyders et al.[32] Under these conditions, a very good diastereoselectively (*de* > 95%) was observed. Thus, (4*S*) isomer **22** was obtained in 84% yield from the cyanide **20**, while from ester **21** the (4*S*) esters **23a** and **24** were obtained in 61% and 70% yields, respectively, with 3-iodo-2-(methoxymethoxy)prop-1-ene (**3**) and 2-chloro-iodopropene (**25**) as the electrophiles. In the case of the alkylation of **21**, the minor (4*R*) isomer **23b** was also isolated (< 5%). The structure of the crystalline product **22** was unambiguously determined by X-ray analysis.[25]

Alkylation of this sugar uronate derivative **21** was hence easily performed in the internal quench condition. It is worth noting that, in our case, alkylation by a sigmatropic uronic acid-drived allyl ketene acetal Ireland Claisen rearrangement[33] could be obtained neither from the corresponding 2-MOM compound nor from the 2-chloroallyl ester, contrarily to the results reported by Rizzacasa[34] et al. and more recently by Thiem et al.[35] from a closely related urono sugar, although unsubstituted allyl esters were used in these two cases.

The nitrile derivative **22** was next transformed into the aldehyde **26** (34% yield) by treatment with DIBAH at −78 °C in toluene. The low yield observed was attributed to difficulties in the total hydrolysis of the iminoaluminate formed during the reduction by use of Rochelle salt or mild acid hydrolysis. Reduction with Raney Nickel by the procedure of Albrecht et al.[36] furnished the aldehyde in 30% yield, with starting nitrile and methyl ketone. In the case of the ester **23a,** reduction with DIBAH produced **26** in 69% yield, but the methyl ketone derivative **28** resulting from the hydrolysis of the enol ether was also isolated (20%), as well as the over-reduced compound **27** (5%). Fortunately, the more stable 2-chloro-allylated ester **24** gave the aldehyde **29** in 70% yield, with only 13% of the other reduced product **30** (Scheme 4).



Scheme 4. Reagents and conditions.: a) CH_2=CH(OMOM)−CH_2I (**3**) or CH_2=CH(Cl)−CH_2I (**25**), KHMDS (0.5 M in toluene), THF at −78 °C; (b) for **22**, **23**, **24** DIBAH in toluene at −78 °C, or Raney Nickel NaH_2PO_2, H_2O, pyridine, CF_3COOH for **22**; (c) for **26:** NBS in aqueous $NaHCO_3$ in dioxane; for **29:** NBS, HBr cat., MeCN/H_2O (4:1); (d) Ph_3P in CH_2Cl_2, propylene oxide, reflux

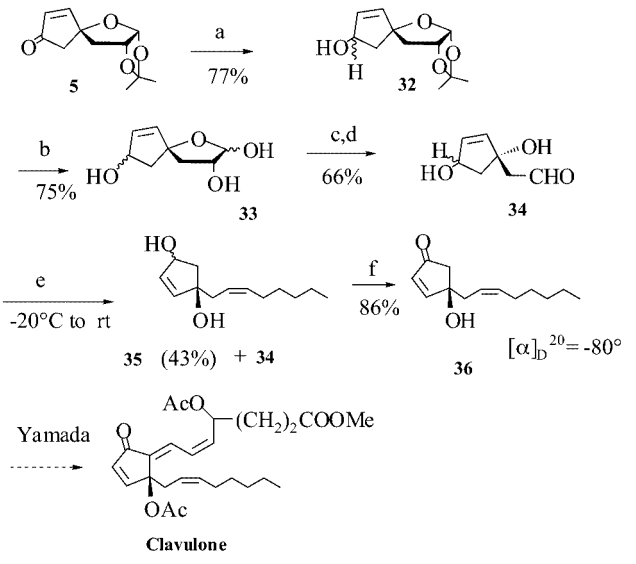
In an attempt to achieve the cyclopentannulation reaction, we first − unsuccessfully −attempted an intramolecular ene reaction by treatment of aldehyde **26** with a Lewis acid (Et_2AlCl, BF_3−Et_2O, $SnCl_4$) in dichloromethane at −78 °C.[37] We also did not succeed in producing a Mannich reaction by treatment of aldehyde **26** with pyrrolidine; this could be attributable to the congested neopentylic position preventing the initial iminium formation. Finally, we adopted an intramolecular Wittig reaction. The enol ethers

26 and **29** were treated with *N*-bromosuccinimide under basic ($NaHCO_3$ in aqueous dioxane) or acidic (cat. HBr in aqueous CH_3CN) conditions, respectively. The not isolated unstable bromoketone intermediate thus obtained (**31**), was directly treated with triphenylphosphane in the presence of propylene oxide as acid scavenger to give, via an intermediary ylide, the cyclopentenone Wittig product **4** (83% from **26** and 66% from **29**).

In summary, by use of this strategy we successfully achieved a stereocontrolled synthesis of the chiral target spiro-furano cyclopentenone **4** in four steps either from nitrile **20** or from glucurono ester **21**. This convenient strategy to synthesize a chiral cyclopentenone was used to prepare clavulone II, a naturally occurring cyclopentenone prostaglandin.

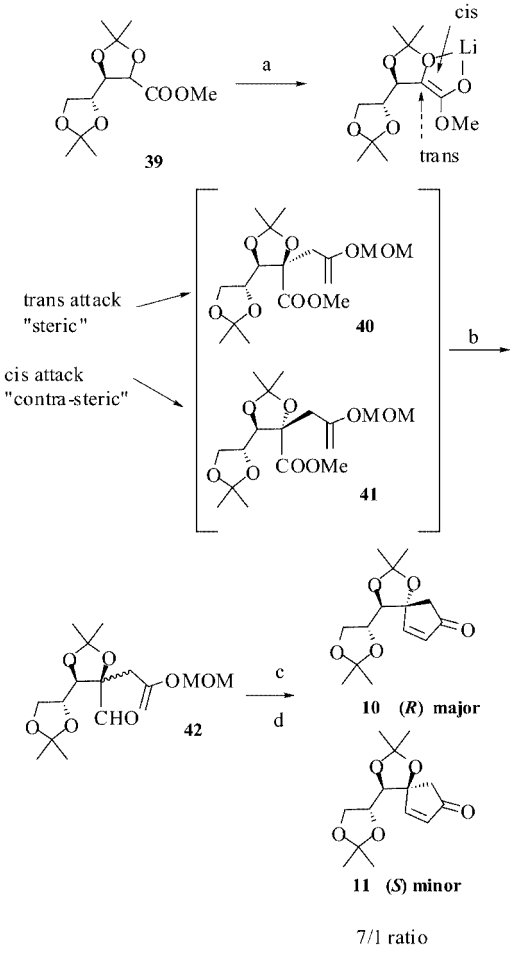
Formal Total Synthesis of Clavulone from Spiro-Furano Cyclopentenone

The reduction of cyclopentenone **5** with Luche reagent[38] gave compound **32**. Acidic hydrolysis of the isopropylidene ring furnished the unsaturated sugar **33** (77%), which was next reduced with sodium borohydride and then oxidized with sodium periodate to give the hemiacetal **34** (66%). Finally, a Wittig reaction with (hexyl)triphenylphosphorane, obtained from (hexyl)triphenylphosphonium bromide and butyllithium at −78 °C, gave the cyclopentanediol **35** (42%). Oxidation of the allylic hydroxy group with Jones reagent furnished the cyclopentenone **36** ($[\alpha]_D^{20} = -80$; $c = 0.5$, $CHCl_3$), identical to the cyclopentenone intermediate of Yamada's clavulone synthesis ($[\alpha]_D^{20} = -84$; $c = 0.31$, $CHCl_3$)[11b,11e] (Scheme 5).



Scheme 5. Reagents and conditions. (a) $NaBH_4$, $CeCl_3 \cdot 7H_2O$, MeOH; (b) $AcOH/H_2O$ (5:2); (c) $NaBH_4$, MeOH; (d) $NaIO_4$, $MeOH/H_2O$; (e) $Ph_3P^+C_6H_{13}Br^-$, BuLi, in THF/HMPA, −20 °C to room temp. (f) Jones, 0 °C

Synthesis of Cyclopentenones by the Highly Stereoselective Alkylation of Dioxolane Ester Enolate: Since the alkylation route to 2-cyclopentenone from urono ester displayed a high diastereoselectivity, an extension of this procedure to the stereoselective synthesis of 2-cyclopentenone by dioxolane ester alkylation was further devised; this should provide a rapid and efficient way to prepare new cyclopentenone prostaglandin analogues (Scheme 6).



Scheme 6. Reagents and conditions. (a) $CH_2{=}CH(MOM){-}CH_2I$ (**3**), KHMDS −78 °C, THF; (b) DIBAH −78 °C in toluene; (c) 1.1 equiv. NBS, aqueous CH_3CN; (d) PPh_3, propylene oxide in aqueous dioxane at reflux

The dioxolane ester **39**, easily prepared from commercial ribonolactone in one step by Chittenden's procedure,[39] was treated with KHMDS in the presence of the 3-iodo-2-(methoxymethoxy)prop-1-ene (**3**) at −78 °C under internal quench conditions, as described previously. The alkylation was very stereoselective and furnished the two products **40** and **41**, in a 7:1 ratio, as determined from the NMR spectrum of the crude reaction mixture (87% *de*). These alkylated compounds were too difficult to separate well and to characterize at this stage. In consequence, they were transformed into cyclopentenones by the intramolecular Wittig reaction sequence. The mixture of compounds **(40 +41)** was treated with DIBAH to give aldehyde **42**, which was cyclized as described previously for compound **26** to give, after column chromatography, the two spiro-cyclopen-

tenones **10** and **11**. The structure of this rigid spiro skeleton could now be determined unambiguously by NOESY experiments. The major compound **10** had a stereogenic quaternary carbon of (*R*) configuration, meaning that the corresponding open-chain alkyl product was **41**, corresponding to an expected *cis* and "contrasteric" attack of the alkylation, in accordance with Hoffmann's observation.[40] The *trans* or "steric" attack was disfavored as a consequence of the 1,3-steric interaction occurring with the incoming electrophile and a methyl group of the dioxolane ring in the sofa transition state.

Conclusion

In conclusion, we have demonstrated that an unprecedented tandem cationic aza-Claisen rearrangement and Mannich cyclization to the synthesis of 4-alkyl-4-hydroxycyclopentenone is an efficient procedure. Application of this reaction to the synthesis of natural prostanoids has been demonstrated, and this reaction could be a good entry point for preparations of series of 4-alkyl-4-hydroxy-2-cyclopentenones. Concurrently, we have studied the stereoselective alkylation of α-alkoxy esters or nitriles, followed by internal Wittig reactions. This sequence of transformations greatly increased the diastereoselectivity of the cyclopentenones formed. These two methodologies are complementary to the one we recently reported in our currently efforts towards the synthesis of new antitumor cyclopentenone prostaglandin analogues.[41]

Experimental Section

General Remarks: Measurements of NMR spectra (90, 250, and 300 MHz, ^{1}H) were made in $CDCl_3$ (which also provided the lock signal at δ = 7.26 ppm) with a Bruker 300 spectrometer. Mass spectra were determined by CI (NH_3 or CH_4). Melting points are uncorrected. Optical rotations were measured with a Perkin−Elmer 241 polarimeter at 25 °C. Silica gel 60 (35−70 μm) was used for flash chromatography, with distilled cyclohexane, ethyl acetate, and dichloromethane being used as eluents. Analytical plates (Merck 60 F_{254} aluminium sheets) were rendered visible by spraying with *p*-anisaldehyde/H_2SO_4/AcOH/EtOH or with phosphomolybdic acid (5% in ethanol), followed by heating. THF was distilled from sodium/benzophenone prior to use. CH_2Cl_2 was distilled from P_2O_5 prior to use. DMF was stored over 4-Å molecular sieves under dry argon atmosphere. Triethylamine was stored under argon atmosphere.

(3′a*R*,5′*S*,6′a*R*)-5: Synthesis from Aldehyde 1 by 3-Aza-Claisen/Mannich Reaction: A solution of **1** (4.8 g, 27.8 mmol) and pyrrolidine (5.05 mL, 61.2 mmol) in a mixture of anhydrous CH_3CN and toluene (1:1, 300 mL) was stirred under argon at 50 °C for 1 h. After evaporation of the solvents under reduced pressure, the residue obtained, a mixture of the (*E* + *Z*) enamine, was dissolved in anhydrous CH_3CN (20 mL). After addition of 3-iodo-2-(methoxymethoxy)prop-1-ene (**3**, 8.4 mL, 55.7 mmol), the reaction mixture was heated at reflux under argon for 22 h at 80 °C. After addition of water and extraction with EtOAc (2 × 50 mL), the collected organic layers were washed with brine, dried over $MgSO_4$, and concentrated. The obtained residue was purified by silica gel flash column chromatography (cyclohexane/EtOAc, 8:1 to 4:1) to afford an oil (2.22 g, 38%) as a mixture of two diastereoisomers in a 3:2 ratio. The pure cyclopentenones were obtained after a second purification of 300 mg by preparative TLC, affording **4** (151 mg) and **5** (101 mg) as solids.

Synthesis from Aldehyde 26: $NaHCO_3$ (350 mg) and NBS (800 mg, 4.5 mmol) were successively added to a solution of aldehyde **26** (1.08 g, 4 mmol) in a CH_3CN/H_2O mixture (5:1, 70 mL). After the mixture had been stirred for 1.5 h, water (20 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 50 mL). The collected organic layers were washed with H_2O and brine, dried ($MgSO_4$), and filtered. The filtrate was cooled to 0 °C; Ph_3P (1.87 g, 7.2 mmol) and propylene oxide (2.5 mL) were then added, and the reaction mixture was heated at reflux for 18 h. After addition of water (100 mL), the mixture was extracted with CH_2Cl_2 (3 × 50 mL). The organic layer was washed with H_2O and brine, and dried ($MgSO_4$). Evaporation by flash column chromatography (cyclohexane/EtOAc, 2:1) gave crystalline **4** (702 mg, 83%).

Synthesis from Aldehyde 29: NBS (562 mg, 3.16 mmol) was added at 0 °C to a cold solution of aldehyde **29** (520 mg, 2.1 mmol) in a CH_3CN/H_2O mixture (4:1, 50 mL), followed by a solution of HBr (48%, 4 μL). The reaction mixture turned yellow and, after stirring for 15 min, the reaction was stopped by addition of a saturated aqueous solution of $NaHCO_3$ until decolorization. The reaction mixture was extracted with CH_2Cl_2 (3 × 30 mL). The collected organic layers were washed with H_2O and brine, dried ($MgSO_4$), and filtered. Ph_3P (2.1 g, 8 mmol) and propylene oxide (1.5 mL) were successively added to the filtrate. The reaction mixture was treated at reflux as above and extracted. Purification by flash column chromatography (cyclohexane/ethyl acetate, 2:1) gave crystalline **4** (250 mg, 66%). **Major Isomer 4 (4′*S*):** $[\alpha]_D^{20} = -17$ (*c* = 0.83, $CHCl_3$). M.p. 68 °C. IR ($CDCl_3$): $\tilde{\nu}_{max}$ (cm^{-1}) = 1680 (C=C), 1723 (C=O). ^{1}H NMR: (250 MHz, $CDCl_3$): δ = 7.81 (d, *J* = 5.7 Hz, 1 H), 6.09 (d, *J* = 5.7 Hz, 1 H), 5.91 (d, *J* = 4 Hz, 1 H), 4.88 (t, *J* = 4 Hz, 1 H), 2.76 and 2.46 (2d, AB system, *J* = 18.5 Hz, 2 H), 2.42 (d, *J* = 14 Hz, 1 H) and 2.25 (dd, *J* = 14, *J* = 5 Hz, 1 H), 1.65 (s, 3 H) and 1.35 (s, 3 H) ppm. MS (CI/NH_3): *m*/*z* = 228 $[M + NH_4]^+$, 211 $[M + H]^+$. $C_{11}H_{14}O_4$ (210.23): calcd. C 62.83, H 6.72; found C 62.74, H 6.72. **Minor Isomer 5 (4′*R*):** $[\alpha]_D^{20} = -84$ (*c* = 1.14, $CHCl_3$). M.p. 94 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.30 (d, *J* = 5.7 Hz, 1 H), 4.92 (t, *J* = 5.7 Hz, 1 H), 2.92 and 2.82 (2d, AB system, *J* = 19 Hz, 2 H), 2.27 (d, *J* = 13.7 Hz, 1 H), 2.17 (dd, *J* = 13.7, *J* = 5 Hz, 1 H), 1.61 (s, 3 H) and 1.37 (s, 3 H) ppm. ^{13}C NMR: (62.5 MHz, $CDCl_3$): δ = 206.2, 162.7, 135.6, 111.8, 106.4, 87.0, 80.9, 49.0, 42.9, 26.3 and 25.5 ppm. MS (CI/NH_3)**:** *m*/*z* = 228 $[M + NH_4]^+$, 211 $[M + H]^+$. $C_{11}H_{14}O_4$ (210.23): calcd. C 62.83, H 6.72; found C 62.66, H 6.57.

Compound 10 [5*R*,4*R*] and Isomer 11 [5*S*,4*R*]. From Aldehyde 9 by 3-Aza-Cope/Mannich Reaction: A solution of **9** (500 mg, 2.17 mmol) and pyrrolidine (0.27 mL, 3.28 mmol) in a mixture of anhydrous CH_3CN/toluene (1:1, 20 mL) was stirred at 50 °C for 1 h. The reaction solvents were evaporated under reduced pressure, and the obtained residue was dissolved in anhydrous CH_3CN (20 mL). 3-iodo-2-(methoxymethoxy)prop-1-ene (**3**, 0.81 mL, 5.40 mmol) was then added. The reaction mixture was stirred at 80 °C for 18 h. After addition of H_2O (10 mL) and extraction with EtOAc (3 × 30 mL), the obtained organic layers were washed with brine, dried over $MgSO_4$, and concentrated to furnish a residue, which was purified by flash column chromatography (cyclohexane/EtOAc, 4:1), giving a mixture of compounds **10** (100 mg) and **11** (107 mg) (36% overall yield from **9**).

From Aldehyde 42: The mixture of aldehyde **42** (160 mg, 1.92 mmol) was treated with $NaHCO_3$ (160 mg) in dioxane (10 mL) and H_2O (0.5 mL). NBS was then added (345 mg). After stirring for 3 h, the reaction mixture was diluted with H_2O (20 mL) and extracted with EtOAc. The collected organic layers were washed with H_2O and with brine, dried ($MgSO_4$), and filtered. The obtained filtrate was evaporated and dissolved in dichloromethane (20 mL). Propylene oxide (0.7 mL) and triphenylphosphane (524 mg) were then added at 0 °C. After stirring for 18 h at room temperature, the reaction mixture was extracted with CH_2Cl_2. The organic layers were washed with H_2O and with brine, and dried ($MgSO_4$). After filtration and evaporation under reduced pressure, the residue obtained was purified by flash column chromatography to give compounds **10** (80 mg, 57%) and **11** (11 mg). **Major Isomer 10 (*R*):** ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.29 (d, *J* = 5.5 Hz, 1 H), 6.19 (d, *J* = 5.5 Hz, 1 H), 4.16−4.08 (m, 2 H), 3.98−3.90 (m, 2 H), 2.95 and 2.35 (2d, AB system, *J* = 18 Hz, 2 H), 1.42, 1.41, 1.27 and 1.24 (4s) ppm. IR: $\tilde{\nu}_{max}$ (cm^{-1}) = 1723 (C=O) ppm. MS (DCI/NH_3): *m*/*z* = 286 $[M + NH_4]^+$, 269 $[M + H]^+$. $C_{14}H_{20}O_5$ (268.31): calcd. C 62.67, H 7.51; found C 62.75, H 7.48. **Minor Isomer 11 (*S*):** $[\alpha]_D^{20}$ = +6 (*c* = 0.5, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.45 (d, *J* = 5.5 Hz, 1 H), 6.25 (d, *J* = 5.5 Hz, 1 H), 4.21−4.10 (m, 1 H), 4.05−3.87 (m, 3 H, H-6, H-7), 2.64 (s, 2 H), 1.50, 1.43, 1.36, 1.25 (4s, 12 H) ppm.

Nonadec-1-ene-3-ol (13): A solution of hexadecyl bromide (4.4 mL, 14.5 mmol) was added dropwise at 0 °C to a suspension of magnesium (350 mg, 14.5 mmol) in anhydrous Et_2O (75 mL), containing a crystal of iodine. The reaction mixture was heated at reflux for 1 h, and was then transferred at 0 °C into a Et_2O (30 mL) solution of acrolein (0.24 mL, 3.6 mmol) and stirred at this temperature for 1 h. The reaction was quenched to neutrality by addition of a 2 N aqueous HCl solution. After addition of water, the reaction mixture was extracted with Et_2O (3 × 50 mL), and the organic layers were washed with water and brine, and dried ($MgSO_4$). After filtration and evaporation under reduced pressure, a residue was obtained, and this was purified by flash column chromatography on silica gel (cyclohexane/ethyl acetate, 10:1) to give compound **13** (530 mg, 52%). ^{1}H NMR (90 MHz, $CDCl_3$): δ = 6.00−5.66 (m, 1 H), 5.35−4.97 (m, 2 H), 4.26−3.97 (m, 1 H), 1.43−1.13 (s, 30 H), 0.86 (t, 3 H) ppm. MS (DCI/NH_3): *m*/*z* = 300 $[M + NH_4]^+$, 283 $[M + H]^+$.

3-(Methoxymethoxy)nonadec-1-ene (14): Compound **13** (500 mg, 1.77 mmol) was dissolved in CH_2Cl_2 (50 mL), and methoxymethyl chloride (0.13 mL, 7 mmol) and *i*Pr_2NEt (0.3 mL, 7 mmol) were then added. The reaction mixture was stirred at room temperature for 24 h. After evaporation under reduced pressure, a residue was obtained, and this was purified by flash column chromatography on silica gel (cyclohexane/ethyl acetate, 15:1) to give compound **14** (400 mg, 69%). ^{1}H NMR (90 MHz, $CDCl_3$): δ = 5.66−5.43 (m, 1 H), 5.30−4.96 (m, 2 H), 4.70 and 4.50 (m), 1.43−1.13 (s, 30 H), 0.86 (t, 3 H) ppm. MS (DCI/NH_3): *m*/*z* = 344 $[M + NH_4]^+$, 327 $[M + H]^+$.

3-(Methoxymethoxy)nonadecane-1,2-diol (15): Compound **14** (390 mg, 1.2 mmol) was dissolved at 0 °C in a mixture of acetone/H_2O (8:1, 36 mL). A solution of OsO_4 in *t*BuOH (1.2 mL, 0.12 mmol) and NMO (140 mg, 1.2 mol) were successively added. The reaction mixture was stirredat room temperature for 18 h , and was then quenched by addition of an aqueous solution of $NaHSO_3$ (10%, 5 mL). After stirring for 1 h, the reaction mixture was extracted with EtOAc (3 × 30 mL). The organic layers were washed with H_2O and brine, and dried ($MgSO_4$). After filtration and evaporation under reduced pressure, a residue was obtained, and this was purified by flash column chromatography on silica gel (cyclohexane/acetone, 3:1), to give compound **15** (400 mg, 93%). ^{1}H NMR (90 MHz, $CDCl_3$): δ = 4.73 and 4.61 (2d, AB system, *J* = 6.9 Hz, 2 H), 3.76−3.50 (m, 4 H), 3.43 (s, 3 H), 1.46 (s, 3 H), 1.28 (s), 0.88 (t) ppm. MS (DCI/NH_3): *m*/*z* = 378 $[M + NH_4]^+$, 361 $[M + H]^+$. $C_{21}H_{44}O_4$ (360.57): calcd. C 69.95, H 12.30; found C 69.87, H 12.32.

2-(Methoxymethoxy)octadecanal (16): A solution of compound **15** (390 mg, 1.05 mmol) in anhydrous benzene (40 mL) was cooled to 0 °C for 5 min, $[Pb(OAc)_4]$ (470 mg, 1.1. mmol) was then added, and the mixture was stirred at room temperature. After 5 min, the yellow suspension became limpid and was filtered through Celite. The filtrate was evaporated, and co-evaporated twice with toluene. The residue obtained was purified by flash column chromatography (cyclohexane/ethyl acetate, 8:1) to give compound **16** (330 mg, 95%). ^{1}H NMR (90 MHz, $CDCl_3$): δ = 9.58 (d, *J* = 1.5 Hz, 1 H), 4.63 (s, 2 H), 3.80 (d, *J* = 1.5 Hz, *J*′ = 6 Hz, 1 H), 1.66−1.06 (m, 30 H), 0.8 (t, 3 H) ppm. MS (DCI/NH_3): *m*/*z* = 346 $[M + NH]^+$. $C_{20}H_{40}O_3$ (328.53): calcd. C 73.12, H 12.27; found C 72.90, H 2.36.

(±)-4-Hexadecyl-4-(methoxymethoxy)cyclopent-2-enone (17): Pyrrolidine (0.3 mL, 3.6 mmol) was added under argon to a solution of aldehyde **16** (330 mg, 1 mmol) in acetonitrile/toluene (1:1, 40 mL). The mixture was stirred at 50 °C for 3 h. After evaporation of the solvents under reduced pressure, dry acetonitrile (30 mL) and iodo compound **3** (0.40 mL, 2.38 mmol) were added. The reaction was stirred at 80 °C for 18 h. The crude residue obtained after evaporation of the solvents under reduced pressure was purified by flash column chromatography (cyclohexane/ethyl acetate, 15:1) to give compound **17** (369 mg, 38%), the starting aldehyde **16** (40 mg, 12%), and compound **18** (60 mg, 19%). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.47 (d, 1 H), 6.19 (d, *J* = 5.7 Hz, 1 H), 4.65 (d, 1 H, AB system) and 4.59 (d, AB system, *J* = 7.5 Hz, 1 H), 3.34 (s, 3 H), 2.65 (d, AB system, *J* = 18.6 Hz, 1 H) and 2.42 (d, AB system, *J* = 18.6 Hz, 1 H), 1.72 (t, *J* = 6.4 Hz, 2 H), 1.24 (s, 28 H), 0.87 (t, *J* = 6 Hz, 3 H) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 206.0, 164.8, 134.3, 91.5, 83.6, 55.0, 45.7, 38.7, 31.6, 29.9, 29.3, 29.2, 29.0, 23.7 and 22.4, 13.8 ppm. MS (DCI/NH_3): *m*/*z* = 384 $[M + NH_4]^+$, 367 $[M + H]^+$. $C_{23}H_{42}O_3$ (366.58): calcd. C 75.36, H 11.55; found C 75.22, H 11.65.

Methoxymethyl Heptadecanoate (18): Side-product obtained during the preparation of **17**. IR: $\tilde{\nu}_{max}$ (cm^{-1}) = 1737. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.23 (s, 2 H), 3.46 (s, 3 H), 2.35 (t, *J* = 7.1 Hz, 2 H), 1.65 (t, *J* = 7.1 Hz, 2 H), 1.26 (s, 26 H), 0.88 (t, *J* = 6.5 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.3, 90.1, 57.4, 34.3, 31.8, 29.6, 29.4, 29.2, 29.1, 29.0, 24.7, 22.6, 14.0 ppm. MS (DCI/NH_3): *m*/*z* = 332 $[M + NH_4]^+$, 315 $[M + H]^+$.

3-Deoxy-1,2-*O*-isopropylidene-4-*C*-[2-(methoxymethoxy)allyl]-β-L-*threo*-pentofurano-urononitrile (22): A solution of KHMDS (0.5 N, 15 mL) was added under argon at −78 °C to a solution of compound **20**[29] (750 mg, 4.43 mmol) and 3-iodo-2-(methoxymethoxy)prop-1-ene (**3**, 1.9 g, 8.38 mmol) in anhydrous THF (30 mL). After stirring for 0.5 h, the reaction mixture was quenched by addition of a saturated aqueous solution of ammonium chloride (5 mL). After addition of water (50 mL), the mixture was extracted with EtOAc (3 × 30 mL). The collected organic layers were washed with brine, and dried with $MgSO_4$. After filtration and evaporation under reduced pressure, a residue was obtained. Purification by flash column chromatography (cyclohexane/EtOAc, 3:1), gave compound **22** (1 g, 84%) as white crystals; m.p. 37−38 °C. $[\alpha]_D^{20}$ = −36 (*c* = 1, $CHCl_3$). IR ($CDCl_3$): $\tilde{\nu}_{max}$ (cm^{-1}) = 1249. ^{1}H NMR (270 MHz, $CDCl_3$): δ = 5.80 (d, *J* = 4 Hz, 1 H), 4.87 (s, 2 H), 4.75

(t, J = 5 Hz, J = 4 Hz, 1 H), 4.35 and 4.20 (2d, AB system, J = 2 Hz, 2 H), 3.40 (s, 3 H), 2.70 and 2.45 (2d, AB system, J = 14 Hz, 2 H), 2.60 (d, J = 14 Hz, 1 H) and 2.10 (dd, J = 14, J' = 5 Hz, 1 H), 1.61 (s, 3 H) and 1.25 (s, 3 H) ppm. MS: (DCI/NH_3): m/z = 287 $[M + NH_4]^+$. $C_{13}H_{19}NO_5$ (269.29): calcd. C 57.98, H 7.11; found C 58.12, H 7.18.

Methyl 3-Deoxy-1,2-*O*-isopropylidene-4-*C*-[2-(methoxymethoxy)-allyl]-β-L-*threo*-pentofurano-uronate (23a) and the Corresponding *erythro* Isomer (23b): The iodo compound **3** (1.5 mL, 4.6 mmol) was added at −78 °C, under argon, to a solution of **21**[29] (460 mg, 2.3 mmol) in anhydrous THF (30 mL). A solution of KHMDS in toluene (0.5 N, 5 mL) was then added dropwise to the mixture. After 0.5 h, the reaction was quenched by addition of a saturated aqueous solution of NH_4Cl (5 mL) and the reaction mixture was extracted with EtOAc (3 × 30 mL). The collected organic layers were washed with water and brine, and dried with $MgSO_4$. After evaporation under reduced pressure, a residue was obtained. Purification by flash chromatography (cyclohexane, EtOAc, 3:1) gave a mixture (420 mg, 61%) of diastereoisomer compounds (4*S*)-*threo*-**23a** (major) and (**4*R*)-*erythro*-23b** (minor) (96% *de*), as shown by crude NMR spectroscopy. Analytical samples of each diastereoisomer were obtained by preparative median pressure liquid chromatography. **(4*S*)-*threo*-23a:** $[\alpha]_D^{20}$ = −56 (c = 1.7, $CHCl_3$). IR ($CDCl_3$)**:** $\tilde{\nu}_{max}$ (cm^{-1}) = 1742. ^1H NMR (90 MHz, $CDCl_3$): δ = 5.82 (d, J = 3.6 Hz, 1 H), 4.87 (s, 2 H), 4.69 (dd, J = J' = 3.6 Hz, 1 H), 4.24 and 4.07 (2d, AB system, J = 2.4 Hz, 2 H), 3.70 (s, 3 H), 3.38 (s, 3 H), 2.82 (d, J = 14 Hz, 1 H), 2.50 (s, 2 H), 1.98 (dd, J = 14, J' = 3.6 Hz, 1 H), 1.40 (s, 3 H), 1.25 (s, 3 H) ppm. MS (DCI/NH_3): m/z = 320 $[M + NH_4]^+$, 303 $[M + H]^+$. $C_{14}H_{22}O_7$ (302.32): calcd. C 55.62, H 7.33; found C 55.48, H 7.15. **(4*R*)-*erythro*-23b:** $[\alpha]_D^{20}$ = −40 (c = 1, $CHCl_3$). ^1H NMR (90 MHz, $CDCl_3$): δ = 5.86 (d, J = 3.75 Hz, 1 H), 4.86 (s, 2 H), 4.73 (m, 1 H), 4.21 and 4.07 (2d, AB system, J = 2.25 Hz, 2 H), 3.75 (s, 3 H), 3.40 (s, 3 H), 2.90 (s, 2 H), 2.40 (m, 2 H), 1.60 (s, 3 H), 1.33 (s, 3 H) ppm. MS (DCI/NH_3): m/z = 320 $[M + NH_4]^+$, 303 $[M + H]^+$.

Methyl 4-*C*-(2-Chloroallyl)- 3-deoxy-1,2-*O*-isopropylidene)-β-L-*threo*-pentofurano-uronate (24): A mixture of compound **21** (2 g, 10 mmol) and iodo derivative **25** (4 mL, 20 mmol) in anhydrous THF (30 mL) was treated at −78 °C with KHMDS (0.5 M in toluene, 20 mL). After 0.5 h, the reaction was worked up as for compound **23a** and **23b**, giving starting ester **21** (0.270 g) and compound **24** (1.33 g, 49%). $[\alpha]_D^{20}$ = −53 (c = 1, $CHCl_3$). IR ($CDCl_3$)**:** $\tilde{\nu}_{max}$ (cm^{-1}) = 1740. ^1H NMR (90 MHz, $CDCl_3$): δ = 5.86 (d, J = 4.5 Hz, 1 H), 5.31 (d, J = 3.75 Hz, 2 H), 4.75 (dd, J = J' = 4.5 Hz, 1 H), 3.80 (s, 3 H), 2.93 (d, J = 15 Hz, 1 H), 2.83 (s, 2 H), 2.10 (dd, J = 4.5, J' = 15 Hz, 1 H), 1.46 (s, 3 H), 1.31 (s, 3 H) ppm. MS (DCI/NH_3): m/z = 294 $[M + NH_4]^+$, 277 $[M + H]^+$. $C_{12}H_{17}ClO_5$ (276.71): calcd. C 52.09, H 6.19; found C 52.20, H 6.15.

3-Deoxy-5-formyl-1,2-*O*-isopropylidene-4-*C*-[2-(methoxymethoxy)-allyl]-β-L-*threo*-pentofuranose (26). From Nitrile 22 by Reduction with DiBAH: A solution of DIBAH in toluene (0.5 mL, 0.75 mmol) was added at −78 °C to a solution of **22** (33 mg, 0.12 mmol) in anhydrous toluene (30 mL). After stirring for 50 min, the reaction was quenched by addition of MeOH (1 mL), a saturated solution of Rochelle salt (5 mL) was then added, and the medium was stirred for 4 h. The reaction mixture was extracted with EtOAc (3 × 20 mL). The collected organic layer were washed with H_2O and with brine, and dried ($MgSO_4$), and the solvents were evaporated under reduced pressure after filtration. The residue obtained was purified by flash chromatography (cyclohexane, EtOAc) to give compound **26** (11.6 mg, 34%) as a colorless oil.

From Nitrile 22 by Reduction with Raney Nickel: A Raney nickel suspension (40%, 10 g) and sodium hypophosphite (1.1 g, 10 mmol) were successively added to a solution of **22** (296 mg, 1.1. mmol) in a pyridine/AcOH/H_2O mixture (2:1/1, v/v, 15 mL). The reaction mixture was stirred under argon at room temp. for 6 h. The filtrate obtained after filtration through Celite was extracted with EtOAc (3 × 30 mL). The collected organic layers were washed with H_2O and with brine, and dried ($MgSO_4$). After filtration and purification under reduced pressure, the obtained residue was purified by flash column chromatography to give compound **26** (90 mg, 34%), together with the starting cyano compound **22** (95 mg, 39%) and the more polar ketone **28** (63 mg, 25%).

From Ester 23a by Reduction with DIBAH: A solution of DIBAH (1.5 M, 3 mL) was added at −78 °C to a solution of **23a** (450 mg, 15 mmol) in anhydrous toluene (50 mL). After stirring for 2 h, the reaction mixture was quenched by addition of MeOH (5 mL), and was then stirred for 0.5 h at 0 °C. A saturated solution of Rochelle salt (10 mL) was added and the mixture was stirred overnight. The reaction mixture was extracted with EtOAc and the collected organic layers were washed with H_2O and with brine, and dried ($MgSO_4$). After filtration and evaporation under reduced pressure, the residue obtained was purified by flash column chromatography (cyclohexane/EtOAc, 3:1) to give compound **26** (280 mg, 69%), compound **28** (70 mg, 20%) and alcohol **27** (15 mg, 5%).

Compound 26: $[\alpha]_D^{20}$ = −48 (c = 0.9, $CHCl_3$). IR ($CDCl_3$): $\tilde{\nu}_{max}$ (cm^{-1}) = 1249 (ether), 1733 (C=O aldehyde), 2956 (=CH_2). ^1H NMR (250 MHz, $CDCl_3$): δ = 9.85 (s, 1 H), 5.97 (d, J = 4 Hz, 1 H, H-1), 4.98 and 4.95 (2d, AB system, J = 14 Hz, 2 H), 4.75 (dd, J = 4, J' = 3 Hz, 1 H), 4.31 and 4.14 (2d, AB system, J = 2 Hz, 2 H), 3.46 (s, 3 H), 2.86 and 2.45 (2d, AB system, J = 14 Hz, , 2 H), 2.73 (d, J = 14 Hz, 1 H) and 2.05 (dd, J = 14, J = 3 Hz, 1 H), 1.49 (s, 3 H) and 1.32 (s, 3 H) ppm. MS (DCI/NH_3): m/z = 290 $[M + NH_4]^+$, 273 $[M + H]^+$.

3-Deoxy-1,2-*O*-isopropylidene-4-*C*-[2-(methoxymethoxy)allyl]-β-L-*threo*-pentofuranose (27): Side-product of the DIBAH reduction of **23a**. $[\alpha]_D^{20}$ = −23 (c = 1, $CHCl_3$). IR ($CDCl_3$)**:** $\tilde{\nu}_{max}$ (cm^{-1}) = 1072, 1262, 2952, 3570. ^1H NMR (250 MHz, $CDCl_3$): δ = 5.80 (d, J = 4.5 Hz, 1 H), 4.90 (s, 2 H), 4.74 (dd, J = 4.5, J' = 4.5 Hz, 1 H), 4.22 and 4.09 (2d, AB system, J = 2 Hz, 2 H), 3.69 (m, 2 H), 3.39 (s, 3 H), 2.49 and 2.30 (2d, AB system, J = 14 Hz, 2 H), 2.40 (m, 1 H), 2.19 (dd, J = 4.5, J' = 15 Hz, 1 H), 2.03 (d, J = 15 Hz, 1 H), 1.52 (s, 3 H), 1.27 (s, 3 H) ppm. ^{13}C NMR (62.5 MHz, CD_3OD): δ = 158.7, 113.2, 107.5, 94.8, 89.6, 88.8, 82.8, 67.2, 56.6, 43.0, 38.0, 27.2 and 26.1 ppm. MS (DCI/NH_3): m/z = 292 $[M + NH_4]^+$. $C_{13}H_{22}O_6$ (274.31): calcd. C 56.92, H 8.08; found C 56.85, H 8.12.

3-Deoxy-5-formyl-1,2-*O*-isopropylidene-4-*C*-(2-oxopropyl)-β-L-*threo*-pentofuranose (28): Side-product of the DIBAH reduction of **23a** or **24**, as well as of the reduction with Raney Nickel of **22**. IR ($CDCl_3$)**:** $\tilde{\nu}_{max}$ (cm^{-1}) = 1249, 1723. ^1H NMR (250 MHz, $CDCl_3$): δ = 10.00 (s, 1 H), 5.90 (d, J = 3.6 Hz, 1 H), 4.70 (t, J = 4.8 Hz, J' = 3.6 Hz, 1 H), 3.13 and 2.82 (2d, AB system, J = 17 Hz, 2 H), 2.58 (d, AB system, J = 14 Hz, 1 H), 2.05 (dd, J = 14, J' = 4.8 Hz, ABX system, 1 H), 1.51 (s, 3 H) and 1.29 (s, 3 H) ppm. MS (DCI/NH_3): m/z = 246 $[M + NH_4]^+$, 229 $[M + H]^+$.

4-*C*-(2-Chloroallyl)-3-deoxy-5-formyl-1,2-*O*-isopropylidene-β-L-*threo*-pentofuranose (29): A solution of DIBAH (1.5 M) in toluene (7 mL, 10.5 mmol) was added dropwise at −78 °C to a solution of compound **24** (1.33 g, 4.8 mmol) in anhydrous toluene (30 mL).

After stirring for 1 h, the reaction was stopped by addition of MeOH (5 mL). Then, after 1 h, a solution of Rochelle salt (30 mL) was added and the mixture was stirred overnight. After addition of H_2O (50 mL), the reaction was extracted with ethyl acetate (3 × 50 mL). The collected organic layers were washed with brine, dried ($MgSO_4$), and filtered. Evaporation and purification by flash chromatography (cyclohexane/ethyl acetate 6:1) gave compound **29** (0.83 g, 70%) and alcohol **30** (170 mg, 13%). $[\alpha]_D^{20} = -54$ (c = 1, $CHCl_3$). IR ($CDCl_3$): $\tilde{\nu}_{max}$ (cm^{-1}) = 1733. ^1H NMR (300 MHz, $CDCl_3$): δ = 9.89 (s, 1 H), 5.93 (d, J = 4 Hz, 2 H), 5.34 (s, 2 H), 4.72 (dd, J = 4, J' = 5 Hz, 1 H), 2.66 (d, J = 14 Hz, 1 H), 2.83 and 2.64 (2d, AB system, J = 15 Hz, 2 H), 2.10 (dd, J = 5, J' = 15 Hz, 1 H), 1.47 (s, 3 H), 1.29 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 203.6, 135.2, 117.7, 111.9, 106.2, 89.8, 79.9, 44.9, 40.0, 26.3 and 25.4 ppm. MS (DCI/NH_3): m/z = 264 $[M + NH_4]^+$, 246 $[M + H]^+$.

4-*C*-(2-Chloroallyl)-3-deoxy-β-1,2-*O*-isopropylidene-L-*threo*-pentofuranose (30): This compound is a side-product of the reduction of **24** with DIBAH. Cf. preparation of **29**. IR ($CDCl_3$)**:** $\tilde{\nu}_{max}$ (cm^{-1}) = 1072−1155, 1262, 2952, 3570. ^1H NMR (250 MHz, $CDCl_3$): δ = 5.80 (d, J = 4.5 Hz, 1 H), 4.90 (s, 2 H), 4.74 (dd, J = 4.5, J' = 4.5 Hz, 1 H), 4.22 and 4.09 (dd, J = 2 Hz, 2 H), 3.69 (m, 2 H), 3.39 (s, 3 H), 2.49 and 2.30 (dd, J = 14 Hz, 2 H), 2.40 (m, 1 H, OH), 2.19 (dd, J = 4.5, J' = 15 Hz, 1 H), 2.03 (d, J = 15 Hz, 1 H), 1.52 (s), 1.27 (s) ppm. ^{13}C NMR (62.5 MHz, CD_3OD): δ = 158.7, 113.2, 107.5, 94.8, 89.6, 88.8, 82.8, 67.2, 56.6, 43.0, 38.0, 27.2 and 26.2 ppm. MS (DCI/NH_3): m/z = 266 $[M + NH_4]^+$. $C_{11}H_{17}ClO_4$ (248.70): calcd. C 53.12, H 6.89; found C 53.01, H 6.80.

(3*R*/*S*,3′a*R*,5′*R*,6′a*R*)-6′,6′a-Dihydro-2′,2′-dimethylspiro[4-cyclopentene-1,5′(3′a*H*)-furo[2,3-*d*][1,3]dioxol]-3-ol (32): Compound **5** (500 mg, 2.4 mmol) was dissolved in a solution of $CeCl_3 \cdot 7H_2O$ (2.5 mmol) in MeOH (6.25 mL), and $NaBH_4$ (94.5 mg, 2.4 mmol) was added dropwise. The reaction mixture was stirred for 5 min at room temperature and then quenched by addition of an saturated aqueous solution of NH_4Cl (5 mL). After addition of water (30 mL), the mixture was extracted with CH_2Cl_2 (3 × 20 mL). The organic layers were washed with brine and dried ($MgSO_4$), and the solvents were evaporated under reduced pressure to give compound **32** (390 mg, 77%) as a mixture of 3*R*/*S* diastereoisomers. ^1H NMR (90 MHz, $CDCl_3$): δ = 5.94 (m, 1 H), 5.77 (d, J = 3 Hz, 1 H), 5.61 (d, J = 4.5 Hz, 1 H), 4.71 (m, 2 H), 2.80 (dd, J = 15, J' = 7.5 Hz, ABX system, 1 H), 2.31−1.81 (m, 3 H), 1.56 (s, 3 H), 1.30 (s, 3 H) ppm. MS: (DCI/NH_3): m/z = 230 $[M + NH_4]^+$, 213 $[M + H]^+$.

(1*R*,3*R*/*S*)-1-(Oct-2-enyl)cyclopent-4-ene-1,3-diol (35): Compound **32** (270 mg, 1.27 mmol) was dissolved in a mixture of AcOH/H_2O (5 mL/3 mL) and stirred for 1 h at 80 °C. Successive evaporations with toluene afforded a residue, which was purified by flash column chromatography on silica gel (MeCN/MeOH, 3%). The crude compound **33** obtained (230 mg) was dissolved in MeOH (10 mL). $NaBH_4$ (50 mg, 1.3 mmol) was added at 0 °C, and after stirring for 15 min, the reaction mixture was neutralized by addition of Amberlite IRC-50S resin. After co-evaporation with MeOH (3 × 10 mL) under reduced pressure, a residue was obtained. This was dissolved in MeOH/H_2O (3:2, 10 mL) and cooled to 0 °C, $NaIO_4$ (278 mg, 130 mmol) was then added, and the mixture was stirred for 1 h at room temperature. After filtration through a Celite pad and evaporation of MeOH under reduced pressure at 30 °C (10 Torr), an aqueous solution of the aldehyde **34** was obtained, giving, after lyophilization, an amorphous solid (110 mg).

Wittig Reaction of Compound 34: HMPA (1 mL) and compound **34** (110 mg) in solution in THF (2 mL) were added at 0 °C to a red solution of (hexyl)triphenylphosphorane in THF [prepared from (*n*-hexyl)triphenylphosphonium bromide (1.27 g, 2.9 mmol in 10 mL of THF at −78 °C), by addition of BuLi (2.5 M in 1.2 mL of THF)]. The reaction mixture was stirred at −20 °C for 15 h and then at room temp. for 6 h. After addition of water (30 mL), the reaction mixture was extracted with Et_2O (3 × 20 mL), and the organic layers were washed with H_2O (5 × 10 mL) and with brine, and dried ($MgSO_4$). Purification by flash column chromatography (cyclohexane/acetone, 5:1) furnished compound **35** (115 mg, 42%). ^1H NMR (250 MHz, $CDCl_3$): δ = 5.91 (m, 2 H, H-4), 5.56 and 5.38 (2m, 2 H), 4.97 (m, 0.33 H), 4.66 (m, 0.66 H), 2.50−2.30 (m, 3 H), 2.08−2.02 (m, 2 H), 2.87−1.69 (m, 3 H), 1.26 (m, 6 H), 0.88 (t, J = 8 Hz, 3 H) ppm. MS (DCI/NH_3): m/z = 228 $[M + NH_4]^+$.

(4*R*)-(*Z*)-4-Hydroxy-4-(oct-2-enyl)cyclopent-2-enone (36): Jones reagent (0.1 mL) was added to a solution of compound **35** (102 mg, 0.48 mmol) in acetone (5 mL). The reaction mixture was stirred for 15 min at room temperature, and the reaction was then stopped by addition of dry sodium bisulfite until a green color was obtained. EtOAc (25 mL) was then added to the reaction mixture. The organic layers were neutralized with aqueous NaOH (0.1 N), washed with brine, and dried ($MgSO_4$), and the solvents were evaporated under reduced pressure to give a residue, which was purified by flash column chromatography on silica gel (cyclohexane/acetone, 7:1). Compound **36** was obtained as an amorphous gum (87 mg, 86%). $[\alpha]_D^{20} = -80$ (c = 0.5, $CHCl_3$). {ref.[11e] $[\alpha]_D^{20} = -84$ (c = 0.31, $CHCl_3$); ref.[11b] $[\alpha]_D^{20} = -54$ (c = 1.52, $CHCl_3$)}. IR ($CDCl_3$)**:** $\tilde{\nu}_{max}$ (cm^{-1}) = 1712. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.43 (d, J = 5.8 Hz, 1 H), 6.15 (d, J = 5.8 Hz, 1 H), 5.67 and 5.37 (2m, 2 H), 2.57 and 2.45 (2d, AB system, J = 18.4 Hz, 2 H, 2.61−2.38 (m, 2 H) ppm. MS: (DCI/NH_3): m/z = 226 $[M + NH_4]^+$, 209 $[M + H]^+$. $C_{13}H_{20}O_2$ (208.30): calcd. C 74.96, H 9.68; found C 74.71, H 9.59.

(5*R*)- and (5*S*)-(1*R*,4*R*) Esters 40 and 41: A solution of ester **39**[39] (2.06 g, 7.9 mmol) and iodopropene **3** (2 mL, 13.2 mmol) in THF (50 mL) was treated at −78 °C with KHMDS (0.5 M, 16 mL) under the same conditions as used for compound **21**. After usual workup, compounds **40** (5*S*) and **41** (5*R*) were obtained as an inseparable mixture of two diastereoisomers (ratio 1:7, respectively). ^1H NMR (90 MHz, $CDCl_3$): δ = 4.88 and 4.78 (2d, AB system, J = 6 Hz, 2 H), 4.22−3.89 (m, 6 H), 3.69 (s, 3 H), 3.37 (s, 3 H), 2.97 and 2.31 (2d, AB system, J = 15 Hz, 2 H), 1.46, 1.43, 1.41 and 1.35 (4s, 12 H) ppm. MS (DCI/NH_3): m/z = 378 $[M + NH_4]^+$, 361 $[M + H]^+$. $C_{17}H_{28}O_8$ (360.40): calcd. C 56.65, H 7.83; found C 56.73, H 7.80.

Carbaldehyde 42: A mixture of **40/41** (920 mg, 2.55 mmol) in toluene (10 mL) was treated at −78 °C with DIBAH (1.5 M, 2.5 mL) and kept stirring for 1.5 h. The reaction mixture was then quenched by addition of MeOH (3 mL) and a saturated aqueous solution of Rochelle salt and extracted with EtOAc (3 × 50 mL). The collected organic layers were washed with H_2O and with brine, and dried ($MgSO_4$). After filtration and evaporation under reduced pressure, a residue was obtained and purified by flash column chromatography (cyclohexane/ethyl acetate, 4:1) to furnish **42** as a mixture of (2*R*) and (2*S*) diastereoisomers (500 mg, 59%) immediately treated (cf. **10** and **11** preparation). ^1H NMR (90 MHz, $CDCl_3$): δ = 9.57 (s, 1 H), 4.90 and 4.80 (2d, AB system, J = 6 Hz, 2 H), 4.29−3.72 (m, 6 H), 3.34 (s, 3 H), 3.03 and 2.40 (2d, AB system, J = 15 Hz, 2 H), 1.45, 1.36, 1.33 and 1.30 (4s, 12 H) ppm. MS: (DCI/NH_3): m/z = 348 $[M + NH_4]^+$, 331 $[M + H]^+$.

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