A General and Highly Efficient Synthesis of Novel Nonactic Acid Analogues

Ludovic Coutable, Christine Saluzzo*

UMR-CNRS 6011, Unité de Chimie Organique Moléculaire et Macromoléculaire, Université du Maine, Avenue Olivier Messiaen, 72085 Le Mans Cedex 9, France
Fax +33(2)43833902; E-mail: christine.saluzzo@univ-lemans.fr

Received 8 April 2008; revised 9 July 2008

Abstract: An efficient enantioselective synthesis of protected nonactic acid analogues, starting from an easily accessible β-keto ester, is described. The key steps of the strategy are asymmetric hydrogenation, chelation-controlled allylation, *cis*-selective etherification, and stereoselective reduction or alkylation of α-halo esters.

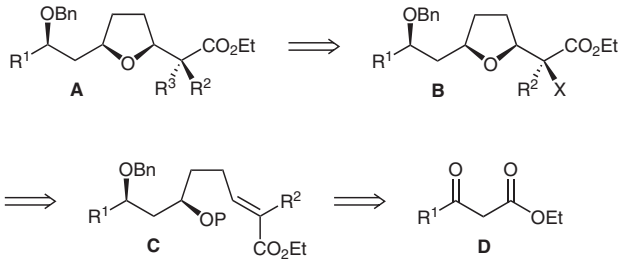
Key words: electrophilic additions, radical reactions, ring closure, stereselective synthesis, total synthesis

The presence of molecules with oxygenated heterocycles in Nature has received considerable attention as a consequence of their capacity in the modification of metallic cations for transport through lipidic membranes. Polyether antibiotics isolated from various *Streptomyces* species possess this property.[1] As structural characteristics, they possess a carboxylate group and 2–5 oxygen atoms serving as ligands for complexation of the cations. Some of them, nactins,[2] feigrisolide C,[3] or pamamycins[4] have been reported to exhibit a wide range of biological activity such as antimicrobial,[2–4] insecticidal,[2] acaricidal,[2] antiprotozoan,[2] antiparasitic,[2] and immunosuppressive[2] effects. Their precursors, nonactic acid or nonactic acid analogues, possess insecticidal and plant stimulation effects.[2] These chiral building blocks can be derived from the chiral pool, or by chemical/enzymatic means from achiral or racemic starting material.[5]

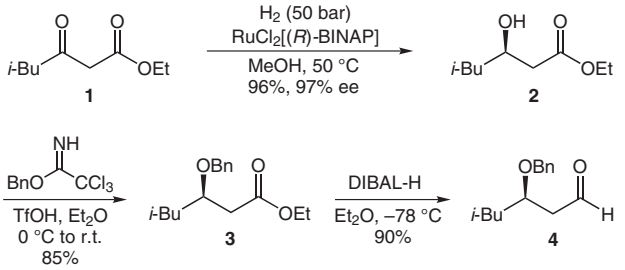
The most efficient synthesis of methyl (benzyloxy)nonactate was performed by Lee and Choi[5g] in seven steps (29% overall yield) starting from (*R*)-3-(benzyloxy)butanal. This approach is based on stereoselective radical cyclization for the construction of the *cis*-2,5-disubstituted tetrahydrofuran ring.

Herein, we report a general and highly stereoselective access to protected analogues of nonactic acid and 2-*epi*-nonactic acid in a nine-step reaction sequence starting from a β-keto ester.

The retrosynthetic analysis of the monomer nonactic acid analogue **A** is depicted in Scheme 1. A radical-mediated dehalogenation or alkylation of the key intermediate **B** was envisaged. The *cis*-2,5-disubstituted tetrahydrofuran **B** could be obtained via Bartlett-type cyclization from the γ,δ-unsaturated ether **C**, which could be synthesized from β-keto ester **D**.



Scheme 1



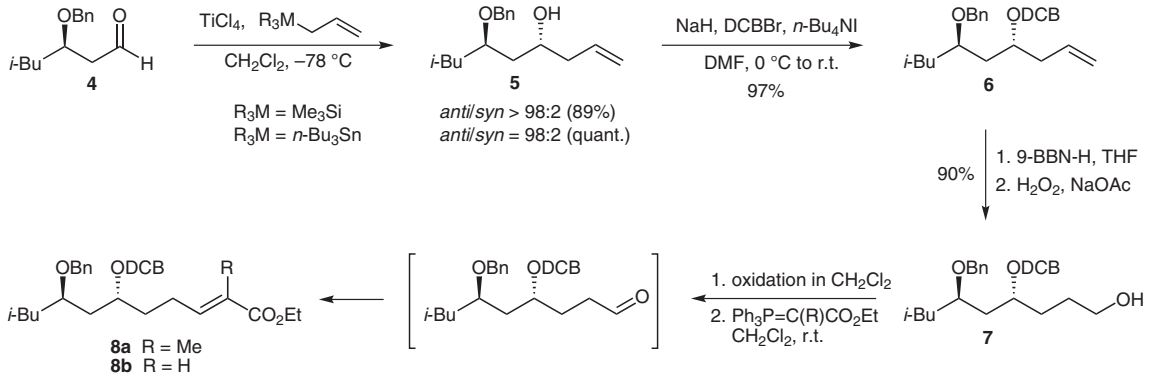
Scheme 2

Our synthesis (Scheme 2) started with the catalytic asymmetric reduction of ethyl 5-methyl-3-oxohexanoate (**1**) obtained by transformation of Meldrum acid.[6] The reduction of this β-keto ester **1**, performed with the Noyori hydrogenation catalyst,[7] gave (*R*)-3-hydroxy ester **2** in 96% yield and 97% ee.[8]

The β-hydroxy ester **2** was then protected as its benzyl ether using benzyl 2,2,2-trichloroacetimidate in the presence of triflic acid.[9] Reduction of the ester function in **3** with diisobutylaluminum hydride at –78 °C in diethyl ether as solvent[10] gave the corresponding β-(benzyloxy)aldehyde **4** in 90% yield.

The diastereoselective allylation of **4** (Scheme 3) was performed using the well-established Reetz et al. procedure.[11] Treatment of aldehyde **4** with either allyltrimethylsilane or allyltributyltin, in the presence of titanium(IV) chloride, led to *anti*-homoallylic alcohol **5**. In both cases, the diastereoselectivity, determined by GC analysis of the crude reaction mixture, was in favor of the *anti* diastereomer (*anti*/*syn* 98:2). Moreover, with the allylsilane, the yield was 89%, in contrast to that obtained with allyltin (quantitative yield). Then, treatment of the alcohol **5** with sodium hydride and 2,6-dichlorobenzyl bromide (DCBBr) in *N*,*N*-dimethylformamide, in the presence of tetrabutylammonium iodide, afforded the cor-

SYNTHESIS 2008, No. 21, pp 3389–3396
Advanced online publication: 16.10.2008
DOI: 10.1055/s-0028-1083185; Art ID: T05508SS



Scheme 3

responding dibenzyl ether **6** in 97% yield.[12] Subsequent hydroboration of the terminal alkene with 9-borabicyclo[3.3.1]nonane in tetrahydrofuran followed by oxidation with hydrogen peroxide/sodium acetate[13] furnished the primary alcohol **7** in 90% yield (Scheme 3).

The bishomoallylic ethers **8a**,**b** were obtained by a one-pot oxidation/olefination protocol[14] and yields ranged from 55 to 69% (Table 1).

On treatment with tetrapropylammonium perruthenate/*N*-methylmorpholine oxide (TPAP/NMO) (Table 1, entry 1) or Dess–Martin periodinane (Table 1, entry 2), followed by Wittig olefination with [1-(ethoxycarbonyl)ethylidene]triphenylphosphorane, compound **7** gave substantially lower yields of compound **8a** than when using the Swern oxidation[15] (Table 1, entry 3). Similar results were observed for the formation of bishomoallylic ether **8b** using *o*-iodoxybenzoic acid (IBX) or Swern conditions, followed by olefination with (ethoxycarbonylmethylene)triphenylphosphorane (Table 1, entries 4, 5). In all cases, the undesired *Z*-isomer was observed, but it was easily removed by column chromatography on silica gel.

To complete the synthesis it was necessary to form the *cis*-2,5-disubstituted tetrahydrofuran ring by halocyclization. The treatment of compounds **8a** or **8b** with iodine[16] or iodine/copper(II) acetate,[17] in acetonitrile at room temperature, was unsuccessful (Table 2, entries 1–3). Nevertheless, the use of better electrophiles iodine monobromide and bromine in dichloromethane at –78 °C led to the cyclization. With iodine monobromide, the bishomoallylic ether **8a** gave the desired compound **9a** in 49% yield together with byproducts (Table 2, entry 4), in contrast to **8b** which furnish the *cis*-2,5-disubstituted tetrahydrofuran **9b** in both excellent yield and diastereoselectivity (Table 2, entry 5). When bromine was employed, the cyclization of **8a** and **8b** was efficient, providing the corresponding *cis*-2,5-disubstituted tetrahydrofurans **10a** and **10b** in good yields and with high diastereoselectivities. The latter can be rationalized by invoking the conformational preference of the intermediate **E**, similar to that proposed by Rychnovsky and Bartlett[16] (Table 2). The 2,5-*cis* relationship was confirmed by NOESY analysis for compounds **9b** and **10b** (Figure 1) and by X-ray analysis for **10a** after dehalogenation and transformation into 3,5-dinitrobenzoate **14** (Scheme 7). Furthermore, the antiperiplanar addition of the oxygen to the double bond activated by the electrophile (IBr or Br_2) results in a product with a 1,2-*anti* relationship between the C–X bond and the newly formed C–O bond as in the intermediate **E** (Table 2).[14,18] To our knowledge, these are the first examples of halocyclization of bishomoallylic ethers containing an unsaturated ester with iodine monobromide and bromine.

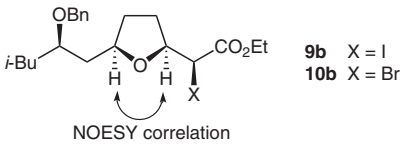


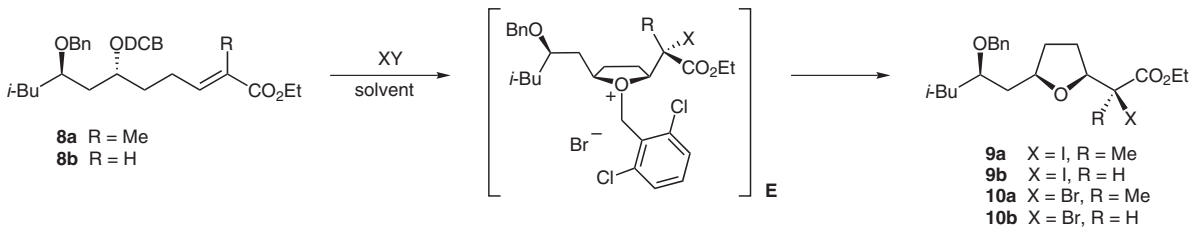
Figure 1

Table 1 One-Pot Oxidation/Olefination Protocol of **7** To Give **8a**,**b**

Entry	Oxidation conditions	R	Product	Yield[a] (%)	Ratio[b] *E*/*Z*
1	TPAP (0.05 equiv), NMO (1.5 equiv), 4Å MS	Me	**8a**	55	nd
2	Dess–Martin periodinane (1.5 equiv)	Me	**8a**	60	nd
3	$(COCl)_2$ (2.2 equiv), DMSO (2.8 equiv), Et_3N (4.9 equiv)	Me	**8a**	69	97:3
4	IBX (1.5 equiv), CH_2Cl_2–acetone (2:1)	H	**8b**	60	nd
5	$(COCl)_2$ (2.2 equiv), DMSO (2.8 equiv), Et_3N (4.9 equiv)	H	**8b**	69	93:7

[a] Yield of isolated product.
[b] Determined by ^1H NMR analysis of the crude mixture; nd = not determined.

Table 2 Halocyclization of **8a**,**b**

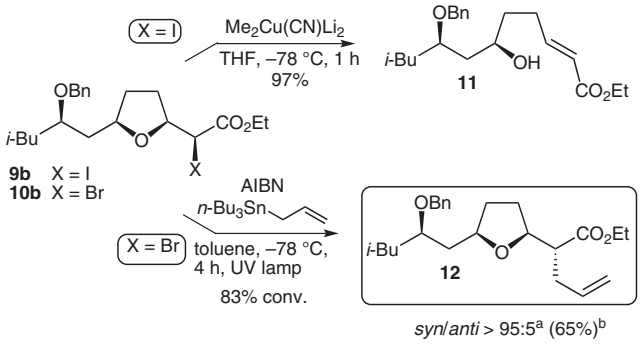


8a R = Me
8b R = H

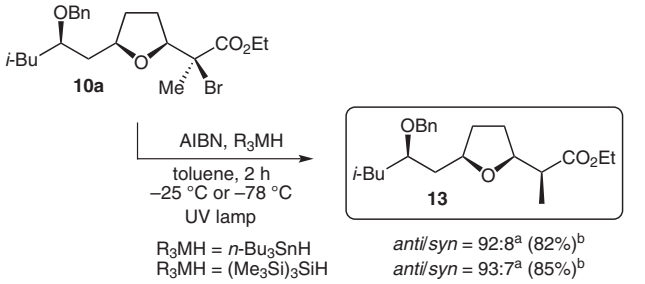
9a X = I, R = Me
9b X = I, R = H
10a X = Br, R = Me
10b X = Br, R = H

Entry	R	XY	Solvent, Temp	Product	Yield[a] (%)	Ratio[b] *cis*/*trans*
1	Me	I_2	MeCN, r.t.	–	–	–
2	H	I_2	MeCN, r.t.	–	–	–
3	H	I_2/$Cu(OAc)_2$	MeCN, r.t.	–	–	–
4	Me	IBr	CH_2Cl_2, –78 °C	**9a**	49	~70:30[c]
5	H	IBr	CH_2Cl_2, –78 °C	**9b**	95	>98:2
6	Me	Br_2	CH_2Cl_2, –78 °C	**10a**	90	>98:2
7	H	Br_2	CH_2Cl_2, –78 °C	**10b**	96	>98:2

[a] Yield of isolated product (detected as a single isomer by ^{1}H NMR analysis).
[b] Determined by ^{1}H NMR analysis of the crude mixture.
[c] Estimated ratio, presence of byproducts.



Scheme 4 Formation of protected 2-*epi*-nonactic acid analogue **12**. [a] Determined by ^{1}H NMR analysis of the crude mixture. [b] Yield of isolated major isomer.



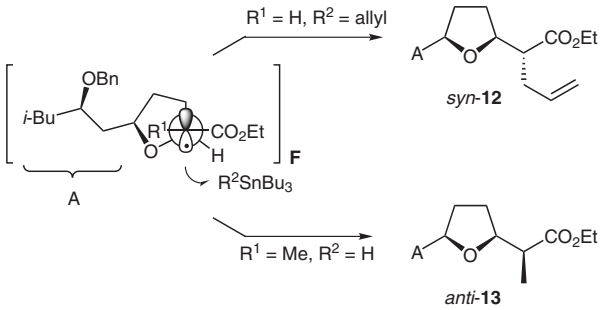
Scheme 5 Radical-mediated reduction of **10a** to give **13**. [a] Determined by ^{1}H NMR analysis of the crude mixture. [b] Yield of isolated major isomer.

Attempts at halogen substitution of the secondary α-iodo ester **9b** with dilithium cyanodimethylcuprate [$Me_2Cu(CN)Li_2$][19] were unsuccessful (Scheme 4). The *E*-isomer **11** resulting from the tetrahydrofuran ring-opening reaction was formed exclusively. Then, the α-bromo ester **10b** was subjected to radical-mediated allylation, according to a modified procedure of Guindon et al.,[20] i.e. UV irradiation was used instead of triethylborane/air for radical initiation. This reaction proceeded smoothly (83% conversion after 4 h) and a ratio higher than 95:5 in favor of the *syn*-isomer was observed. Thus, the first protected 2-*epi*-nonactic acid analogue **12** was isolated in 65% yield.

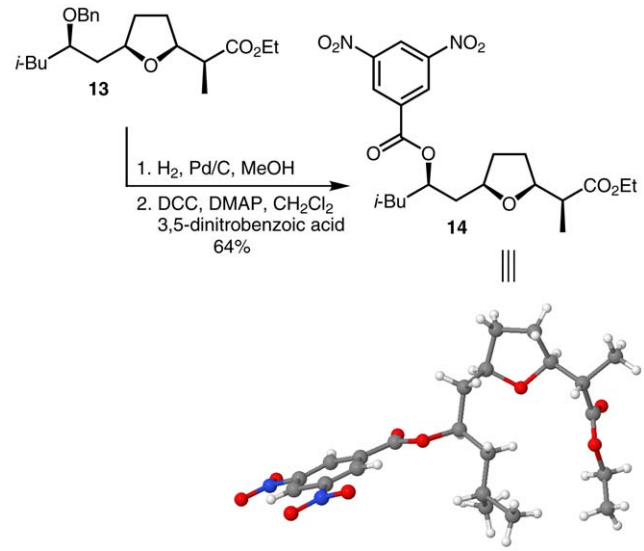
For the tertiary α-bromo ester **10a**, radical-mediated reduction[20] was realized (Scheme 5). Treatment of compound **10a** with tributyltin hydride at –78 °C or with tris(trimethylsilyl)silane at –25 °C, in the presence of a catalytic amount of 2,2′-azobis(isobutyronitrile) under UV irradiation (366 nm), led to the desired dehalogenated compound **13**, in 82% and 85% isolated yields, respectively. In both cases, similar stereoselectivities were observed.

The diastereoselectivity of the radical reactions would be explained by considering the mechanism via the radical intermediate **F** (Scheme 6).[21] The conformation of this intermediate, which takes into consideration both steric and electronic factors, led to the preferential approach of the reagent to the bottom face of the π-system.

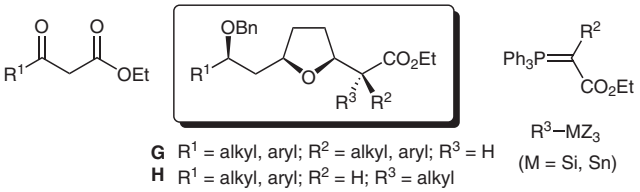
In order to confirm the stereoselectivity of the radical processes and the relative configuration of the stereocenters, X-ray analysis has been performed on a derivative of compound **13** (Scheme 7). The dinitrobenzoate ester **14** was prepared by debenzylation of **13** followed by esterification with 3,5-dinitrobenzoic acid in the presence of *N*,*N*′-dicyclohexylcarbodiimide and 4-(dimethylamino)pyridine. X-ray analysis of compound **14** confirmed the stereochemical outcome in the reactions.



Scheme 6



Scheme 7



Scheme 8

In summary, we have reported a total stereoselective synthesis of two protected nonactic acid analogues from a β-keto ester in nine steps, with 27% overall yield for analogue **12** and 33% for **13**. The key steps of the synthetic sequence are asymmetric hydrogenation, chelation-controlled allylation, *cis*-cyclo haloetherification, followed by a radical-mediated allylation or dehalogenation; all the reactions are highly stereocontrolled. Moreover, this versatile approach offers a general access to nonactic and 2-*epi*-nonactic acid analogues **G** and **H**, respectively (Scheme 8).

The structural variations come from easily accessible building blocks: β-keto ester, ylide, and allylic organometallic reagent. Moreover, introduction of such an allyl group, highly tunable, allows the preparation of a wide range of nonactic and 2-*epi*-nonactic acid analogues.

All commercial materials were used without further purification unless otherwise noted. Et_2O and THF were distilled over Na/benzophenone ketyl. CH_2Cl_2, toluene, DMF, and DMSO were distilled from CaH_2. All reactions were performed under a dry argon atmosphere in oven-dried glassware. Flash chromatography was performed on Merck silica gel (40–63 μm). Analytical TLC was carried out on Merck silica gel $60F_{254}$. Optical rotations were measured with a Perkin Elmer 343 polarimeter at the Na D line with a 1-dm path length, 1-mL cell. NMR spectra were recorded on a Bruker AC400 and are referenced to TMS as internal standard. IR spectra were recorded on a Nicolet Avatar 370 DTGS infrared spectrophotometer. Elemental analyses were performed by the Service de Microanalyse de l'Institut de Chimie des Substances Naturelles, Gif-sur-Yvette. HRMS were recorded on a Waters Micromass GCT Premier. Chiral GC was performed on a HP 6890 with He as carrier gas and using a Rt-βDEX cst column (30 m, 0.25 mm i.d., 0.25 μm). Radical-mediated reactions were carried out using a Hamamatsu UV spot light source (200 W type L8222-01).

Ethyl (*R*)-3-Hydroxy-5-methylhexanoate (2)

(*R*)-BINAP (53 mg, 0.084 mmol) and $[RuCl_2(benzene)]_2$ (20 mg, 0.04 mmol) were dissolved in degassed DMF (1.4 mL) under argon. The mixture was heated to 100 °C for 10 min. After cooling to 50 °C, the solvent was removed under vacuum to give the catalyst as an orange-red solid. This catalyst (5 mg) was dissolved in a degassed soln of **1** (1.72 g, 10 mmol) in MeOH (1.5 mL). The mixture was transferred to an autoclave, which was then purged with H_2 (3 ×). The mixture was stirred overnight at 50 °C under a pressure of 50 bar. After carefully venting the H_2 at r.t., the solvent was removed and the residue dissolved in Et_2O. The ether soln was filtered through a pad of silica gel. Evaporation of the solvent gave the pure **2** as a colorless oil; yield: 1.67 g (96%); 97% ee (GC).

$[\alpha]_D^{20}$ –12.9 (*c* 8.00, $CHCl_3$).

Ethyl (*R*)-3-(Benzyloxy)-5-methylhexanoate (3)

To a stirred soln of **2** (870 mg, 5 mmol) and benzyl 2,2,2-trichloroacetimidate (2.53 g, 10 mmol) in Et_2O (10 mL) was added, at 0 °C, TfOH (44 μL, 0.5 mmol). The mixture was allowed to warm to r.t. and stirred overnight. After concentration, the residue was taken up with cyclohexane and the crystalline trichloroacetamide removed by filtration. The filtrate was washed with brine, dried ($MgSO_4$), and concentrated. The crude mixture was purified by flash chromatography (cyclohexane–EtOAc, 95:5) to give **3** as a colorless oil; yield: 1.12 g (85%).

$[\alpha]_D^{20}$ +10.0 (*c* 1.00, $CHCl_3$).

IR (film): 3089, 3065, 3031, 2956, 2870, 1950, 1877, 1736, 1603, 1496, 1466, 1454, 1368, 1307, 1240, 1179, 1096, 1069, 1029, 735, 697 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 0.89 (d, *J* = 6.6 Hz, 3 H), 0.91 (d, *J* = 6.6 Hz, 3 H), 1.25 (t, *J* = 7.2 Hz, 3 H), 1.29 (ddd, *J* = 13.9, 8.1, 5.0 Hz, 1 H), 1.60 (ddd, *J* = 13.9, 8.0, 5.8 Hz, 1 H), 1.7–1.9 (m, 1 H), 2.46 (dd, *J* = 15.0, 5.7 Hz, 1 H), 2.62 (dd, *J* = 15.0, 6.8 Hz, 1 H), 3.9–4.0 (m, 1 H), 4.14 (q, *J* = 7.2 Hz, 1 H), 4.15 (q, *J* = 7.2 Hz, 1 H), 4.51 (d, *J* = 11.3 Hz, 1 H), 4.58 (d, *J* = 11.3 Hz, 1 H), 7.2–7.4 (m, 5 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.1, 22.2, 23.1, 24.5, 40.2, 44.1, 60.3, 71.4, 74.4, 127.5, 127.7, 128.2, 138.4, 171.7.

Anal. Calcd for $C_{16}H_{24}O_3$: C, 72.69; H, 9.15. Found: C, 72.73; H, 9.27.

(*R*)-3-(Benzyloxy)-5-methylhexanal (4)

To a stirred soln of **3** (793 mg, 3 mmol) in Et_2O (6 mL) was added dropwise, at –78 °C, 1 M DIBAL-H in toluene (4.2 mL, 4.2 mmol) and stirring was continued at –78 °C for at least 1 h. Upon complete consumption of the ester, the reaction was quenched with 2 M HCl (12 mL) and the temperature allowed to warm up to r.t.. The aqueous phase was separated and extracted with Et_2O (2 ×). The combined organic extracts were washed with brine, dried ($MgSO_4$), and concentrated. The residue was purified by flash chromatography (cyclohexane–EtOAc, 9:1) to give **4** as a colorless oil; yield: 596 mg (90%).

$[\alpha]_D^{20}$ +4.10 (*c* 24.9, $CHCl_3$).

IR (film): 3089, 3064, 3031, 2956, 2928, 2870, 2726, 1951, 1875, 1724, 1604, 1497, 1467, 1454, 1386, 1367, 1354, 1308, 1244, 1207, 1171, 1142, 1096, 1069, 1028, 737, 698 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 0.91 (d, *J* = 6.5 Hz, 3 H), 0.92 (d, *J* = 6.5 Hz, 3 H), 1.32 (ddd, *J* = 13.8, 7.6, 5.7 Hz, 1 H), 1.66 (ddd, *J* = 13.8, 7.5, 6.3 Hz, 1 H), 1.7–1.8 (m, 1 H), 2.59 (ddd, *J* = 16.2, 5.1, 2.0 Hz, 1 H), 2.67 (ddd, *J* = 16.2, 6.5, 2.6 Hz, 1 H), 3.9–4.1 (m, 1 H), 4.53 (d, *J* = 11.3 Hz, 1 H), 4.54 (d, *J* = 11.3 Hz, 1 H), 7.2–7.4 (m, 5 H), 9.82 (dd, *J* = 2.6, 2.0 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.3, 22.8, 24.4, 43.8, 48.4, 71.0, 72.6, 127.5, 127.6, 128.2, 138.0, 201.4.

Anal. Calcd for $C_{14}H_{20}O_2$: C, 76.33; H, 9.15. Found: C, 76.38; H, 9.05.

(4*R*,6*R*)-6-(Benzyloxy)-8-methylnon-1-en-4-ol (5); General Procedure

To a stirred soln of **4** (1.0 equiv) in CH_2Cl_2 (10 mL/mmol) was added, at –78 °C, $TiCl_4$ (freshly distilled over Cu, 1.0 equiv). After 2 min, allyl reagent (1.2 equiv) was added dropwise and stirring was continued at –78 °C for at least 30 min. Upon complete consumption of aldehyde, the mixture was quenched with sat. aq NH_4Cl and the temperature allowed to warm up to r.t. The aqueous phase was separated and extracted with CH_2Cl_2 (2 ×). The combined organic extracts were washed with brine, dried ($MgSO_4$), and concentrated. The residue was purified by flash chromatography (cyclohexane–EtOAc, 95:5) to give **5** as a colorless oil.

The general procedure was used with the following reagent amounts: **4** (980 mg, 4.45 mmol), CH_2Cl_2 (45 mL), $TiCl_4$ (488 μL, 4.45 mmol), and allyltributyltin (1.65 mL, 5.34 mmol). Yield: 1.17 g (quant.).

The general procedure was used with the following reagent amounts: **4** (3.64 g, 16.5 mmol), CH_2Cl_2 (165 mL), $TiCl_4$ (1.81 mL, 16.5 mmol), and allyltrimethylsilane (3.15 mL, 19.8 mmol). Yield: 3.87 g (89%).

$[\alpha]_D^{20}$ –25.6 (*c* 2.00, $CHCl_3$).

IR (film): 3443, 3067, 3031, 2955, 2928, 2869, 1948, 1826, 1641, 1605, 1497, 1467, 1454, 1433, 1385, 1366, 1308, 1246, 1207, 1170, 1147, 1090, 1068, 1028, 997, 914, 868, 845, 816, 735, 697 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 0.90 (d, *J* = 6.3 Hz, 6 H), 1.2–1.4 (m, 1 H), 1.58 (ddd, *J* = 14.7, 6.5, 2.4 Hz, 1 H), 1.6–1.8 (m, 2 H), 1.76 (ddd, *J* = 14.7, 9.6, 3.5 Hz, 1 H), 2.2–2.3 (m, 2 H), 2.88 (d, *J* = 3.0 Hz, 1 H), 3.78 (m, 1 H), 3.9–4.1 (m, 1 H), 4.56 (s, 2 H), 5.09 (dm, *J* = 10.5 Hz, 1 H), 5.10 (dm, *J* = 16.8 Hz, 1 H), 5.83 (ddt, *J* = 16.8, 10.5, 7.1 Hz, 1 H), 7.2–7.4 (m, 5 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.8, 22.9, 24.7, 39.4, 42.2, 42.9, 67.7, 71.1, 75.5, 117.4, 127.7, 127.9 (2 C), 128.4 (2 C), 134.9, 138.3.

Anal. Calcd for $C_{17}H_{26}O_2$: C, 77.82; H, 9.99. Found: C, 77.77; H, 9.94.

(4*R*,6*R*)-6-(Benzyloxy)-4-(2,6-dichlorobenzyloxy)-8-methylnon-1-ene (6)

To a suspension of NaH (60% dispersion in mineral oil, 64 mg, 1.60 mmol) in DMF (6.5 mL) was added, at 0 °C, a soln of **5** (210 mg, 0.80 mmol) in DMF (0.7 mL). The mixture was stirred at 0 °C for 20 min and a soln of 2,6-dichlorobenzyl bromide (395 mg, 1.60 mmol) in DMF (1.3 mL) was added slowly, followed by Bu_4NI (59 mg, 0.16 mmol) at 0 °C. The resulting mixture was stirred overnight at r.t., then quenched with sat. aq NH_4Cl and diluted with Et_2O. The aqueous phase was separated and the organic layer was washed with H_2O and brine, dried ($MgSO_4$), and concentrated. The residue was purified by flash chromatography (cyclohexane–EtOAc, 95:5) to give the **6** as a colorless oil; yield: 328 mg (97%).

$[\alpha]_D^{20}$ –54.4 (*c* 0.80, $CHCl_3$).

IR (film): 3067, 3030, 2954, 2868, 1945, 1864, 1722, 1640, 1582, 1564, 1496, 1467, 1454, 1437, 1385, 1365, 1306, 1247, 1198, 1147, 1094, 1065, 1028, 994, 914, 853, 826, 778, 767, 733, 697 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 0.88 (d, *J* = 6.5 Hz, 3 H), 0.89 (d, *J* = 6.5 Hz, 3 H), 1.26 (ddd, *J* = 13.6, 6.8, 6.8 Hz, 1 H), 1.53 (ddd, *J* = 13.6, 6.7, 6.7 Hz, 1 H), 1.6–1.7 (m, 2 H), 1.6–1.8 (m, 1 H), 2.4–2.5 (m, 2 H), 3.69 (m, 1 H), 3.7–3.8 (m, 1 H), 4.23 (d, *J* = 11.3 Hz, 1 H), 4.46 (d, *J* = 11.3 Hz, 1 H), 4.73 (d, *J* = 10.5 Hz, 1 H), 4.84 (d, *J* = 10.5 Hz, 1 H), 5.08 (dm, *J* = 10.1 Hz, 1 H), 5.11 (dm, *J* = 17.1 Hz, 1 H), 5.88 (ddt, *J* = 17.1, 10.1, 7.1 Hz, 1 H), 7.12 (dd, *J* = 8.5, 7.6 Hz, 1 H), 7.2–7.4 (m, 7 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.9, 23.1, 24.6, 38.3, 40.5, 43.9, 65.1, 70.8, 74.7, 75.1, 117.3, 127.3, 127.5 (2 C), 128.2–128.3 (4 C), 129.8, 133.8, 134.4, 136.8 (2 C), 139.1.

HRMS (CI+, methane): *m*/*z* $[M + H]^+$ calcd for $C_{24}H_{31}Cl_2O_2$: 421.1701; found: 421.1696.

(4*R*,6*R*)-6-(Benzyloxy)-4-(2,6-dichlorobenzyloxy)-8-methylnonan-1-ol (7)

To a stirred soln of **6** (1.85 g, 4.41 mmol) in THF (20 mL) was added dropwise, at 0 °C, 0.5 M 9-BBN-H in THF (26.4 mL, 13.2 mmol). The mixture was stirred at 0 °C for 1 h and at r.t. overnight. The mixture was cooled to 0 °C, EtOH (3.9 mL), sat. aq NaOAc (13.4 mL) and 30% H_2O_2 (4.3 mL) were added in that order; stirring was continued at 0 °C for 1 h and at r.t. for 5 h. The mixture was diluted with Et_2O (150 mL), washed with H_2O (2×), sat. aq $NaHCO_3$ and sat. aq NH_4Cl, dried ($MgSO_4$), and concentrated. The residue was purified by flash chromatography (cyclohexane–EtOAc, 8:2) to give **7** as a colorless oil; yield: 1.76 g (90%).

$[\alpha]_D^{20}$ –47.2 (*c* 1.00, $CHCl_3$).

IR (film): 3404, 3088, 3064, 3030, 2951, 2924, 2868, 1946, 1865, 1806, 1582, 1564, 1496, 1468, 1454, 1436, 1385, 1365, 1247, 1197, 1171, 1146, 1094, 1059, 993, 854, 826, 778, 767, 733, 697 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 0.90 (d, *J* = 6.6 Hz, 3 H), 0.90 (d, *J* = 6.6 Hz, 3 H), 1.27 (ddd, *J* = 13.7, 6.7, 6.7 Hz, 1 H), 1.5–1.8 (m, 9 H), 3.6–3.7 (m, 3 H), 3.7–3.8 (m, 1 H), 4.26 (d, *J* = 11.3 Hz, 1 H), 4.49 (d, *J* = 11.3 Hz, 1 H), 4.73 (d, *J* = 10.4 Hz, 1 H), 4.79 (d, *J* = 10.4 Hz, 1 H), 7.14 (dd, *J* = 8.5, 7.6 Hz, 1 H), 7.2–7.4 (m, 7 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.9, 23.1, 24.6, 27.9, 30.2, 40.3, 43.8, 63.0, 65.1, 70.8, 74.9, 75.6, 127.3, 127.6 (2 C), 128.2–128.4 (4 C), 129.8, 133.7, 136.8 (2 C), 138.9.

Anal. Calcd for $C_{24}H_{32}Cl_2O_3$: C, 65.60; H, 7.34. Found: C, 65.54; H, 7.31.

Oxidation/Olefination Reaction; General Procedure

To a stirred soln of oxalyl chloride (2.2 equiv) in CH_2Cl_2 (15 mL/mmol) was added dropwise, at –78 °C, DMSO (2.8 equiv), then the resulting mixture was stirred for 30 min. Subsequently, a soln of **7** (1 equiv) in CH_2Cl_2 (4 mL/mmol) was added over 5 min giving a

white precipitate. After stirring at –78 °C for 10 min, Et_3N (4.9 equiv) was added. After 15 min, the mixture was allowed to warm up to 0 °C and stirred for 1 h. Then, the ylide (1.5 equiv) was added at 0 °C, and the resultant mixture stirred at r.t. overnight. The mixture was diluted with Et_2O (10 mL/mmol), washed with H_2O (2 ×) and brine, then dried ($MgSO_4$), and concentrated. The residue was taken up with cyclohexane and filtered. The filtrate was evaporated to afford a yellowish oil. Purification by flash chromatography (cyclohexane–EtOAc, 95:5) gave the pure (*E*)-bishomoallylic ether **8**.

Ethyl (2*E*,6*R*,8*R*)-8-(Benzyloxy)-6-(2,6-dichlorobenzyloxy)-2,10-dimethylundec-2-enoate (8a)

Following the general procedure using oxalyl chloride (1.51 mL, 17.6 mmol), DMSO (1.59 mL, 22.4 mmol), **7** (3.52 g, 8.00 mmol), Et_3N (5.40 mL, 38.9 mmol), CH_2Cl_2 (150 mL), and $Ph_3P{=}C(Me)CO_2Et$ (4.35 g, 12.0 mmol) gave **8a** as a colorless oil; yield: 2.86 g (69%).

$[\alpha]_D^{20}$ –28.9 (*c* 1.10, $CHCl_3$).

IR (film): 3088, 3064, 3030, 2954, 2928, 2869, 1947, 1865, 1712, 1650, 1582, 1564, 1496, 1466, 1454, 1437, 1386, 1366, 1273, 1261, 1196, 1135, 1094, 1075, 1029, 993, 918, 855, 826, 779, 767, 736, 697 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 0.90 (d, *J* = 6.6 Hz, 3 H), 0.91 (d, *J* = 6.6 Hz, 3 H), 1.2–1.4 (m, 1 H), 1.30 (t, *J* = 7.1 Hz, 3 H), 1.5–1.7 (m, 2 H), 1.6–1.8 (m, 4 H), 1.84 (s, 3 H), 2.2–2.4 (m, 2 H), 3.6–3.8 (m, 2 H), 4.19 (q, *J* = 7.1 Hz, 2 H), 4.27 (d, *J* = 11.3 Hz, 1 H), 4.49 (d, *J* = 11.3 Hz, 1 H), 4.72 (d, *J* = 10.4 Hz, 1 H), 4.78 (d, *J* = 10.4 Hz, 1 H), 6.77 (tm, *J* = 7.4 Hz, 1 H), 7.14 (dd, *J* = 8.5, 7.5 Hz, 1 H), 7.2–7.4 (m, 7 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.3, 14.3, 22.9, 23.1, 24.0, 24.6, 32.7, 40.4, 43.9, 60.3, 65.1, 70.8, 74.8, 75.3, 127.3, 127.6 (2 C), 128.0, 128.2–128.4 (4 C), 129.8, 133.7, 136.8 (2 C), 138.9, 141.8, 168.1.

Anal. Calcd for $C_{29}H_{38}Cl_2O_4$: C, 66.79; H, 7.34. Found: C, 66.77; H, 7.25.

Ethyl (2*E*,6*R*,8*R*)-8-(Benzyloxy)-6-(2,6-dichlorobenzyloxy)-10-methylundec-2-enoate (8b)

Following the general procedure using oxalyl chloride (1.83 mL, 21.4 mmol), DMSO (1.93 mL, 27.2 mmol), **7** (4.27 g, 9.70 mmol), Et_3N (6.54 mL, 47.2 mmol), CH_2Cl_2 (180 mL), and $Ph_3P{=}CHCO_2Et$ (5.08 g, 14.6 mmol) gave **8b** as a colorless oil; yield: 3.42 g (69%).

$[\alpha]_D^{20}$ –27.0 (*c* 1.00, $CHCl_3$).

IR (film): 3063, 3030, 2952, 2928, 2871, 1949, 1870, 1718, 1654, 1572, 1442, 1363, 1311, 1268, 1201, 1167, 1095, 1064, 986, 854, 774, 736, 700 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 0.90 (d, *J* = 6.6 Hz, 3 H), 0.91 (d, *J* = 6.6 Hz, 3 H), 1.2–1.4 (m, 1 H), 1.29 (t, *J* = 7.1 Hz, 3 H), 1.5–1.7 (m, 2 H), 1.6–1.8 (m, 4 H), 2.2–2.4 (m, 2 H), 3.6–3.8 (m, 2 H), 4.19 (q, *J* = 7.1 Hz, 2 H), 4.29 (d, *J* = 11.3 Hz, 1 H), 4.50 (d, *J* = 11.3 Hz, 1 H), 4.70 (d, *J* = 10.3 Hz, 1 H), 4.75 (d, *J* = 10.3 Hz, 1 H), 5.84 (dm, *J* = 15.6 Hz, 1 H), 6.98 (dt, *J* = 15.6, 6.9 Hz, 1 H), 7.14 (dd, *J* = 8.5, 7.5 Hz, 1 H), 7.2–7.4 (m, 7 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.3, 22.9, 23.1, 24.6, 27.4, 32.2, 40.4, 43.9, 60.1, 65.1, 70.8, 74.8, 75.1, 121.4, 127.4, 127.6 (2 C), 128.3–128.4 (4 C), 129.9, 133.6, 136.8 (2 C), 138.9, 148.9, 166.6.

Anal. Calcd for $C_{28}H_{36}Cl_2O_4$: C, 66.27; H, 7.15. Found: C, 66.37; H, 7.16.

Electrophilic Cyclization; General Procedure

Method A: To a stirred soln of **8** (1.0 equiv) in CH_2Cl_2 (50 mL/mmol) was added slowly, at –78 °C, 0.5 M IBr in CH_2Cl_2 (freshly prepared by mixing equimolar quantities of I_2 and Br_2 in anhyd CH_2Cl_2, 1.4–1.5 equiv). The resulting brown soln was stirred in the dark at –78 °C. After complete consumption of the starting material, the mixture was quenched with sat. aq $Na_2S_2O_3$ soln and diluted with Et_2O. The aqueous phase was separated and extracted with Et_2O (2 ×). The combined organic extracts were washed with brine, dried ($MgSO_4$), and concentrated. The residue was purified by flash chromatography (cyclohexane–EtOAc, 95:5) to give the α-iodotetrahydrofuran **9**.

Method B: To a stirred soln of **8** (1.0 equiv) in CH_2Cl_2 (50 mL/mmol) was added slowly, at –78 °C, a 1.0 M soln of Br_2 in CH_2Cl_2 (freshly prepared, 1.4–2.0 equiv). The resulting brown soln was stirred in the dark at –78 °C. After complete consumption of the starting material, the mixture was quenched with sat. aq $Na_2S_2O_3$ and diluted with Et_2O. The aqueous phase was separated and extracted with Et_2O (2 ×). The combined organic extracts were washed with brine, dried ($MgSO_4$), and concentrated. The residue was purified by flash chromatography (cyclohexane–EtOAc, 95:5) to give the α-bromotetrahydrofuran **10**.

Ethyl (2*S*)-2-{(2*S*,5*R*)-5-[(2*R*)-2-(Benzyloxy)-4-methylpentyl]tetrahydrofuran-2-yl}-2-iodopropanoate (9a)

Following the general procedure, method A, using **8a** (261 mg, 0.50 mmol) and IBr soln (1.5 mL, 0.75 mmol) gave **9a** as a colorless oil; yield: 120 mg (49%).

IR (film): 3088, 3064, 3030, 2955, 2869, 1949, 1873, 1732, 1604, 1585, 1564, 1497, 1467, 1454, 1385, 1366, 1298, 1259, 1212, 1173, 1088, 1067, 1029, 910, 862, 806, 736, 698 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 0.88 (d, *J* = 6.6 Hz, 6 H), 1.2–1.3 (m, 1 H), 1.29 (t, *J* = 7.1 Hz, 3 H), 1.4–1.6 (m, 2 H), 1.6–1.8 (m, 3 H), 1.84 (s, 3 H), 1.9–2.3 (m, 3 H), 3.5–3.7 (m, 1 H), 4.0–4.2 (m, 1 H), 4.24 (q, *J* = 7.1 Hz, 2 H), 4.42 (dd, *J* = 8.0, 5.7 Hz, 1 H), 4.51 (s, 2 H), 7.2–7.4 (m, 5 H).

Ethyl (2*S*)-2-{(2*S*,5*R*)-5-[(2*R*)-2-(Benzyloxy)-4-methylpentyl]tetrahydrofuran-2-yl}-2-iodoacetate (9b)

Following the general procedure, method A, using **8b** (135 mg, 0.27 mmol) and IBr soln (740 μL, 0.37 mmol) gave **9b** as a colorless oil; yield: 120 mg (95%).

$[\alpha]_D^{20}$ –69.0 (*c* 1.00, $CHCl_3$).

IR (film): 3062, 3030, 2953, 2870, 1952, 1877, 1736, 1606, 1459, 1366, 1300, 1260, 1195, 1129, 1088, 1065, 1035, 929, 894, 857, 804, 740, 698 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 0.88 (d, *J* = 6.6 Hz, 3 H), 0.89 (d, *J* = 6.6 Hz, 3 H), 1.2–1.4 (m, 1 H), 1.28 (t, *J* = 7.1 Hz, 3 H), 1.53 (ddd, *J* = 13.6, 6.8, 6.8 Hz, 1 H), 1.59 (m, 1 H), 1.6–1.8 (m, 3 H), 1.94 (m, 1 H), 1.9–2.1 (m, 1 H), 2.22 (m, 1 H), 3.5–3.7 (m, 1 H), 4.15 (d, *J* = 9.2 Hz, 1 H), 4.21 (q, *J* = 7.1 Hz, 2 H), 4.1–4.3 (m, 1 H), 4.27 (ddd, *J* = 9.2, 7.3, 5.1 Hz, 1 H), 4.51 (s, 2 H), 7.2–7.4 (m, 5 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.8, 22.8, 23.0, 24.6, 26.1, 31.1, 31.4, 42.2, 44.3, 61.7, 71.5, 75.2, 78.6, 79.7, 127.4, 127.8 (2 C), 128.3 (2 C), 138.9, 170.0.

HRMS (CI+, methane): *m*/*z* $[M + H]^+$ calcd for $C_{21}H_{32}IO_4$: 475.1345; found: 475.1352.

Anal. Calcd for $C_{21}H_{31}IO_4$: C, 53.17; H, 6.59. Found: C, 53.11; H, 6.61.

Ethyl (2*S*)-2-{(2*S*,5*R*)-5-[(2*R*)-2-(Benzyloxy)-4-methylpentyl]tetrahydrofuran-2-yl}-2-bromopropanoate (10a)

Following the general procedure, method B, using **8a** (2.86 g, 5.49 mmol) and Br_2 soln (7.69 mL, 7.69 mmol) gave **10a** as a colorless oil; yield: 2.18 g (90%).

$[\alpha]_D^{20}$ –26.4 (*c* 1.00, $CHCl_3$).

IR (film): 3088, 3064, 3030, 2955, 2869, 1949, 1875, 1739, 1604, 1460, 1366, 1263, 1213, 1173, 1070, 963, 910, 862, 806, 735, 698 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 0.88 (d, *J* = 6.6 Hz, 6 H), 1.26 (ddd, *J* = 13.6, 7.3, 6.2 Hz, 1 H), 1.29 (t, *J* = 7.1 Hz, 3 H), 1.4–1.6 (m, 2 H), 1.6–1.8 (m, 3 H), 1.84 (s, 3 H), 1.9–2.1 (m, 2 H), 2.0–2.2 (m, 1 H), 3.5–3.7 (m, 1 H), 4.11 (m, 1 H), 4.24 (q, *J* = 7.1 Hz, 2 H), 4.42 (dd, *J* = 8.0, 5.6 Hz, 1 H), 4.51 (s, 2 H), 7.2–7.4 (m, 5 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.8, 22.6, 22.7, 22.8, 24.5, 28.3, 31.9, 41.0, 44.2, 61.8, 61.9, 71.3, 75.1, 78.0, 81.9, 127.3, 127.7 (2 C), 128.1 (2 C), 138.8, 170.3.

Anal. Calcd for $C_{22}H_{33}BrO_4$: C, 59.86; H, 7.54. Found: C, 59.88; H, 7.52.

Ethyl (2*S*)-2-{(2*S*,5*R*)-5-[(2*R*)-2-(Benzyloxy)-4-methylpentyl]tetrahydrofuran-2-yl}-2-bromoacetate (10b)

Following the general procedure, method B, using **8b** (519 mg, 1.02 mmol) and Br_2 soln (2.05 mL, 2.05 mmol) gave **10b** as a colorless oil; yield: 420 mg (96%).

$[\alpha]_D^{20}$ –49.7 (*c* 1.00, $CHCl_3$).

IR (film): 3088, 3064, 3030, 2954, 2867, 1950, 1877, 1747, 1604, 1586, 1497, 1465, 1454, 1385, 1368, 1305, 1266, 1197, 1145, 1067, 1028, 939, 893, 853, 806, 736, 698 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 0.89 (d, *J* = 6.6 Hz, 6 H), 1.26 (ddd, *J* = 13.6, 7.1, 6.3 Hz, 1 H), 1.29 (t, *J* = 7.1 Hz, 3 H), 1.53 (ddd, *J* = 13.6, 6.7, 6.7 Hz, 1 H), 1.5–1.7 (m, 1 H), 1.6–1.8 (m, 3 H), 1.9–2.1 (m, 2 H), 2.1–2.3 (m, 1 H), 3.5–3.7 (m, 1 H), 4.00 (d, *J* = 8.9 Hz, 1 H), 4.1–4.3 (m, 1 H), 4.23 (q, *J* = 7.1 Hz, 1 H), 4.24 (q, *J* = 7.1 Hz, 1 H), 4.37 (ddd, *J* = 8.8, 7.3, 4.6 Hz, 1 H), 4.50 (d, *J* = 11.4 Hz, 1 H), 4.51 (d, *J* = 11.4 Hz, 1 H), 7.2–7.4 (m, 5 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.9, 22.8, 22.9, 24.5, 29.4, 31.3, 42.0, 44.3, 47.9, 61.8, 71.4, 75.2, 78.2, 79.0, 127.4, 127.8 (2 C), 128.2 (2 C), 138.8, 168.5.

Anal. Calcd for $C_{21}H_{31}BrO_4$: C, 59.02; H, 7.31. Found: C, 59.01; H, 7.23.

Ethyl (2*E*,6*R*,8*R*)-8-(Benzyloxy)-6-hydroxy-10-methylundec-2-enoate (11)

In a dry Schlenk flask was placed CuCN (41 mg, 0.46 mmol). The vessel was flushed with argon and then evacuated under high vacuum; the process being repeated three times. Anhyd THF (2 mL) was introduced and the slurry cooled to –78 °C. To this slowly stirring suspension was added dropwise 1.6 M MeLi in THF (575 μL, 0.92 mmol). The heterogeneous mixture was allowed to warm up gradually until complete dissolution and was then recooled to –78 °C. A soln of **10b** (98 mg, 0.23 mmol) in THF (1 mL) was introduced and the resulting mixture was stirred at –78 °C for 1 h. The reaction was quenched with a mixture composed of 10% concd NH_4OH–90% sat. aq NH_4Cl soln and diluted with Et_2O. The aqueous phase was separated and the organic layer was washed with brine, dried ($MgSO_4$), and concentrated to give **11** as a colorless oil; yield: 77 mg (97%).

IR (film): 3493, 3089, 3064, 3031, 2954, 2869, 1949, 1877, 1807, 1709, 1654, 1497, 1466, 1454, 1386, 1367, 1269, 1183, 1132, 1094, 1069, 1029, 914, 849, 745, 698 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 0.90 (d, *J* = 6.1 Hz, 6 H), 1.2–1.4 (m, 1 H), 1.29 (t, *J* = 7.1 Hz, 3 H), 1.5–1.9 (m, 6 H), 2.1–2.5 (m, 2 H), 3.03 (br s, 1 H), 3.7–4.0 (m, 2 H), 4.19 (q, *J* = 7.1 Hz, 2 H), 4.54 (s, 2 H), 5.83 (dm, *J* = 15.6 Hz, 1 H), 6.98 (dt, *J* = 15.6, 6.9 Hz, 1 H), 7.2–7.4 (m, 5 H).

Ethyl (2*R*)-2-{(2*S*,5*R*)-5-[(2*R*)-2-(Benzyloxy)-4-methylpentyl]tetrahydrofuran-2-yl}pent-4-enoate (12)

To a stirred and degassed soln of **10b** (200 mg, 0.47 mmol) and AIBN (15 mg, 0.09 mmol) in anhyd toluene (4.7 mL) was added dropwise, at –78 °C, allyltributyltin (150 μL, 0.94 mmol). The mixture was irradiated for 4 h with a UV lamp (366 nm) and then quenched with sat. aq NH_4Cl soln and diluted with EtOAc. The aqueous phase was separated and the organic layer was dried ($MgSO_4$) and concentrated. The residue was purified by flash chromatography (cyclohexane–EtOAc, 95:5) to give **12** as a colorless oil; yield: 119 mg (65%).

$[\alpha]_D^{20}$ –33.5 (*c* 0.40, $CHCl_3$).

IR (film): 3065, 3030, 2955, 2870, 1949, 1876, 1732, 1642, 1605, 1497, 1465, 1454, 1368, 1340, 1304, 1259, 1181, 1156, 1069, 1029, 996, 915, 855, 804, 735, 698 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 0.89 (d, *J* = 6.6 Hz, 3 H), 0.90 (d, *J* = 6.6 Hz, 3 H), 1.25 (t, *J* = 7.1 Hz, 3 H), 1.28 (ddd, *J* = 13.6, 7.3, 6.0 Hz, 1 H), 1.4–1.6 (m, 2 H), 1.6–1.7 (m, 2 H), 1.7–1.8 (m, 2 H), 1.9–2.1 (m, 2 H), 2.4–2.6 (m, 3 H), 3.6–3.7 (m, 1 H), 3.9–4.1 (m, 2 H), 4.13 (q, *J* = 7.1 Hz, 1 H), 4.13 (q, *J* = 7.1 Hz, 1 H), 4.54 (s, 2 H), 5.00 (ddd, *J* = 10.2, 1.8, 1.2 Hz, 1 H), 5.07 (ddd, *J* = 17.1, 1.8, 1.6 Hz, 1 H), 5.78 (dddd, *J* = 17.1, 10.2, 7.2, 6.4 Hz, 1 H), 7.2–7.4 (m, 5 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.3, 22.8, 23.0, 24.6, 29.3, 31.5, 34.2, 41.9, 44.4, 51.7, 60.2, 71.5, 75.4, 76.5, 78.9, 116.5, 127.4, 127.9 (2 C), 128.3 (2 C), 135.4, 139.0, 173.4.

HRMS (CI+, methane): *m/z* $[M + H]^+$ calcd for $C_{24}H_{37}O_4$: 389.2692; found: 389.2709.

Ethyl (2*S*)-2-{(2*S*,5*R*)-5-[(2*R*)-2-(Benzyloxy)-4-methylpentyl]tetrahydrofuran-2-yl}propanoate (13); General Procedure

To a stirred and degassed soln of **10a** (1.0 equiv) and AIBN (0.02–0.15 equiv) in anhyd toluene (10 mL/mmol) was added dropwise, at –78 °C, R_3MH (1.5–2.0 equiv). The mixture was irradiated for 2 h with a UV lamp (366 nm) and then concentrated. The residue was taken up with cyclohexane (10 mL/mmol) and treated with 1 M TBAF in THF (2.5 equiv) at r.t. for 5 min. After filtration of the mixture through a short pad of silica gel and solvent removal, a residue was obtained and subsequently purified by flash chromatography (cyclohexane–EtOAc, 95:5) to yield, as a colorless oil, the major isomer **13**.

The general procedure was used with the following reagent amounts: **10a** (673 mg, 1.52 mmol), AIBN (5 mg, 0.03 mmol), toluene (15 mL), and *n*-Bu_3SnH (819 μL, 3.04 mmol). Yield: 450 mg (82%).

The general procedure was used with the following reagent amounts: **10a** (221 mg, 0.50 mmol), AIBN (12 mg, 0.08 mmol), toluene (5 mL), and $(Me_3Si)_3SiH$ (233 μL, 0.75 mmol). Yield: 153 mg (85%).

$[\alpha]_D^{20}$ –9.30 (*c* 1.00, $CHCl_3$).

IR (film): 3088, 3064, 3030, 2954, 2870, 1948, 1876, 1732, 1604, 1497, 1455, 1368, 1332, 1300, 1259, 1188, 1157, 1067, 1029, 952, 905, 862, 806, 736, 698 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 0.88 (d, *J* = 6.5 Hz, 3 H), 0.90 (d, *J* = 6.5 Hz, 3 H), 1.11 (d, *J* = 7.0 Hz, 3 H), 1.26 (t, *J* = 7.1 Hz, 3 H), 1.27 (ddd, *J* = 13.6, 7.5, 5.9 Hz, 1 H), 1.4–1.8 (m, 6 H), 1.9–2.1 (m, 2 H), 2.50 (dq, *J* = 8.2, 7.0, 1 H), 3.5–3.7 (m, 1 H), 4.0–4.1 (m, 2 H), 4.15 (q, *J* = 7.1 Hz, 1 H), 4.15 (q, *J* = 7.1 Hz, 1 H), 4.51 (d, *J* = 11.3 Hz, 1 H), 4.53 (d, *J* = 11.3 Hz, 1 H), 7.2–7.4 (m, 5 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.3, 14.2, 22.7, 23.0, 24.6, 28.6, 31.5, 41.8, 44.5, 45.6, 60.2, 71.6, 75.4, 76.5, 80.3, 127.3, 127.8 (2 C), 128.2 (2 C), 139.0, 174.9.

Anal. Calcd for $C_{22}H_{34}O_4$: C, 72.89; H, 9.45. Found: C, 72.68; H, 9.43.

Ethyl 2-(5-{2-[3,5-Dinitrobenzyloxy]-4-methylpentyl}tetrahydrofuran-2-yl)propanoate (14)

A mixture of the **13** (110 mg, 0.30 mmol) and 10% Pd-C (64 mg) in MeOH (3 mL) was stirred at r.t. for 4 h under H_2 (1 bar). The solid was filtered off and washed with EtOAc. The filtrate was evaporated under reduced pressure. To a soln of this crude alcohol (27 mg, 0.10 mmol), 3,5-dinitrobenzoic acid (25 mg, 0.12 mmol), and DMAP (24 mg, 0.20 mmol) in CH_2Cl_2 (1 mL) was added slowly, at 0 °C, a soln of DCC (23 mg, 0.11 mmol) in CH_2Cl_2 (0.5 mL). The mixture was allowed to warm up to r.t. and stirred overnight, then concentrated. The residue was taken up with Et_2O, filtered, and concentrated. Flash chromatography (cyclohexane–EtOAc, 95:5) afforded **14** as white crystals; yield: 30 mg (64%); mp 48–50 °C.

IR (film): 3105, 2959, 2873, 1731, 1629, 1598, 1548, 1462, 1345, 1277, 1172, 1075, 921, 825, 773, 730, 722 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 0.96 (d, *J* = 6.5 Hz, 6 H), 1.08 (d, *J* = 7.0 Hz, 3 H), 1.26 (t, *J* = 7.1 Hz, 3 H), 1.4–1.7 (m, 4 H), 1.75 (ddd, *J* = 13.7, 8.2, 5.8 Hz, 1 H), 1.8–2.1 (m, 4 H), 2.45 (dq, *J* = 8.2, 7.0 Hz, 1 H), 3.9–4.1 (m, 2 H), 4.13 (q, *J* = 7.1 Hz, 2 H), 5.4–5.5 (m, 1 H), 9.1–9.3 (m, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.3, 14.2, 22.3, 22.9, 24.8, 28.4, 31.4, 41.0, 43.8, 45.5, 60.3, 74.3, 75.8, 80.7, 122.1, 129.4 (2 C), 134.5, 148.6 (2 C), 162.0, 174.7.

HRMS (FI): *m*/*z* $[M]^+$ calcd for $C_{22}H_{30}N_2O_9$: 466.1951; found: 466.1949.

Acknowledgment

We are grateful to Dr. Karim Adil for carrying out the crystal structure determination of compound **14**. The authors thank the CNRS for financial support and the Ministère de la Recherche for L. C. graduate fellowship.

References

(1) Faul, M. M.; Huff, B. E. *Chem. Rev.* **2000**, *100*, 2407.
(2) Žižka, Z. *Folia Microbiol.* **1998**, *43*, 7.
(3) (a) Sobolevskaya, M. P.; Fotso, S.; Havash, U.; Denisenko, V. A.; Helmke, E.; Prokofeva, N. G.; Kuznetsova, T. A.; Laatsch, H.; Elyakov, G. B. *Chem. Nat. Compd.* **2004**, *40*, 282. (b) Tang, Y.-Q.; Sattler, I.; Thiericke, R.; Grabley, S.; Feng, X.-Z. *J. Antibiot.* **2000**, *53*, 934.
(4) (a) Kang, E. J.; Lee, E. *Chem. Rev.* **2005**, *105*, 4348. (b) Metz, P. *Top. Curr. Chem.* **2005**, *244*, 215.
(5) (a) Fleming, I.; Ghosh, S. K. *Stud. Nat. Prod. Chem.* **1996**, *18*, 229. (b) Ferraz, H. M. C.; Payret-Arrúa, M. E. *Quim. Nova* **1998**, *21*, 597. (c) Kiyota, H.; Abe, M.; Ono, Y.; Oritani, T. *Synlett* **1997**, 1093. (d) Mandville, G.; Girard, C.; Bloch, R. *Tetrahedron* **1997**, *53*, 17079. (e) Meiners, U.; Cramer, E.; Frohlich, R.; Wibbeling, B.; Metz, P. *Eur. J. Org. Chem.* **1998**, 2073. (f) Ahmar, M.; Duyck, C.; Fleming, I. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2721. (g) Lee, E.; Choi, S. J. *Org. Lett.* **1999**, *1*, 1127. (h) Wang, Y.; Metz, P. *Tetrahedron: Asymmetry* **2000**, *11*, 3995. (i) Fraser, B.; Perlmutter, P. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2896. (j) Jeong, J. W.; Woo, B. Y.; Ha, D. C.; No, Z. *Synlett* **2003**, 393. (k) Wu, Y.; Sun, Y.-P. *Org. Lett.* **2006**, *8*, 2831.
(6) (a) Oikawa, Y.; Sugano, O.; Yonemitsu, J. *J. Org. Chem.* **1978**, *43*, 2087. (b) Houghton, R. P.; Lapham, D. J. *Synthesis* **1982**, 451.
(7) (a) Noyori, R.; Ohkuma, T.; Kitamura, M. *J. Am. Chem. Soc.* **1987**, *109*, 5856. (b) Noyori, R.; Ohkuma, T. *Angew. Chem. Int. Ed.* **2001**, *40*, 40.
(8) (a) Jernelius, J. A.; Schrock, R. R.; Hoveyda, A. M. *Tetrahedron* **2004**, *60*, 7345. (b) Baraldi, P. T.; Zarbin, P. H. G.; Vieira, P. C.; Corrêa, A. G. *Tetrahedron: Asymmetry* **2002**, *13*, 621.
(9) Nakajima, N.; Horita, K.; Abe, R.; Yonemitsu, O. *Tetrahedron Lett.* **1988**, *29*, 4139.
(10) Enders, D.; von Berg, S.; Jandeleit, B. *Org. Synth., Coll. Vol. X*; John Wiley & Sons: London, **2002**, 177.
(11) Reetz, M. T.; Kesseler, K.; Jung, A. *Tetrahedron Lett.* **1984**, *25*, 729.
(12) White, J. D.; Wang, G.; Quaranta, L. *Org. Lett.* **2003**, *5*, 4109.
(13) Suenaga, K.; Araki, K.; Sengoku, T.; Uemura, D. *Org. Lett.* **2001**, *3*, 527.
(14) Guindon, Y.; Soucy, F.; Yoakim, C.; Ogilvie, W. W.; Plamondon, L. *J. Org. Chem.* **2001**, *66*, 8992.
(15) Cossy, J.; Willis, C.; Bellosta, V.; Bouzbouz, S. *J. Org. Chem.* **2002**, *67*, 1982.
(16) Rychnovsky, S. D.; Bartlett, P. A. *J. Am. Chem. Soc.* **1981**, *103*, 3963.
(17) Sanseverino, A. M.; da Silva, F. M.; Jones, J. Jr.; de Mattos, M. C. S. *J. Braz. Chem. Soc.* **2000**, *11*, 381.
(18) Chamberlin, A. R.; Mulholland, R. L. Jr.; Kahn, S. D.; Hehre, W. J. *J. Am. Chem. Soc.* **1987**, *109*, 672.
(19) Lipshutz, B. H.; Wilhelm, R. S. *J. Am. Chem. Soc.* **1981**, *103*, 7672.
(20) Guindon, Y.; Lavallée, J.-F.; Boisvert, L.; Chabot, C.; Delorme, D.; Yoakim, C.; Hall, D.; Lemieux, R.; Simoneau, B. *Tetrahedron Lett.* **1991**, *32*, 27.
(21) Reviews: (a) Porter, N. A.; Giese, B.; Curran, D. P. *Acc. Chem. Res.* **1991**, *24*, 296. (b) Radical allylation: Smadja, W. *Synlett* **1994**, 1. (c) Radical reduction: Guindon, Y.; Guérin, B.; Chabot, C.; Mackintosh, N.; Ogilvie, W. W. *Synlett* **1995**, 449. (d) Guindon, Y.; Faucher, A.-M.; Bourque, E.; Caron, V.; Jung, G.; Landry, S. R. *J. Org. Chem.* **1997**, *62*, 9276.