Pergamon

SCIENCE DIRECT®

Tetrahedron 59 (2003) 10181–10186

TETRAHEDRON

From furan to open-chain systems. Synthesis of C1–C9 fragment of tylonolide

Jerzy Raczko[a,b,*]

[a]*RD Chemipan, Institute of Physical Chemistry, Polish Academy of Sciences, Kasprzaka 44/52, 01-224 Warsaw, Poland*
[b]*Institute of Organic Chemistry, Polish Academy of Sciences, Kasprzaka 44/52, 01-224 Warsaw, Poland*

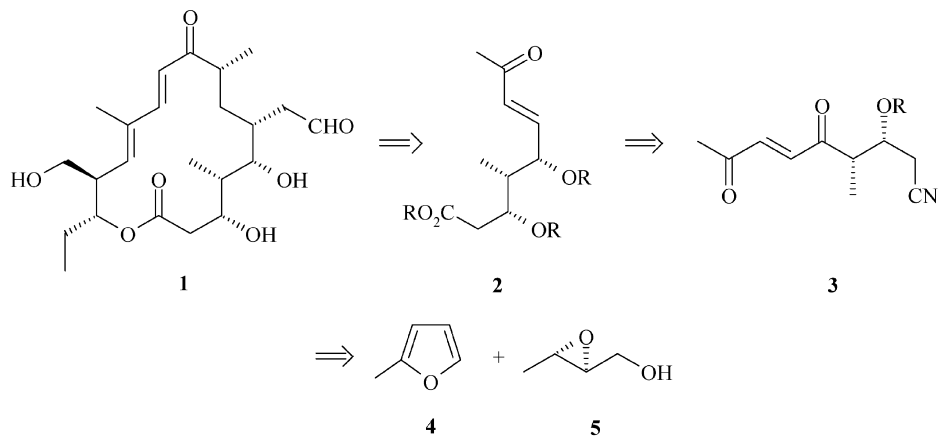
Received 29 August 2003; revised 2 October 2003; accepted 23 October 2003

Abstract—Stereoselective synthesis of C1–C9 subunit of macrocyclic lactone—tylonolide is presented. Starting from 2-methylfuran and crotyl alcohol, a 2,5-disubstituted furan derivative was synthesized. Its oxidation leads to α,β-unsaturated dicarbonyl intermediate which has been transformed into acyclic fragment bearing five consecutive asymmetric centers.

The macrolide antibiotics have been the subject of extensive research for over two decades.[1] The synthetic efforts directed towards these complex structures have resulted in progress of important methodologies in particular acyclic stereocontrol. Tylosin is a typical 16-membered ring macrolide antibiotic that is used therapeutically in veterinary medicine. Tylonolide **1**, the aglycon of tylosin, has been the object of synthetic efforts by several research groups.[2,3]

In continuing our studies on application of furan derivatives in organic synthesis we have attempted the stereoselective synthesis of the right wing of this molecule using the furan ring as a convenient C-4 elongation unit.[4] The eastern C-9 fragment, being the object of our studies, can be obtained by condensation of 2-methylfuran with the epoxide **5**, derived from crotyl alcohol, and C-1 homologation of resulting diol. Oxidative transformation of the furan ring leads to acyclic enedione **3** which is easy to functionalize on both carbonyl groups, and conjugated double bond (Scheme 1).

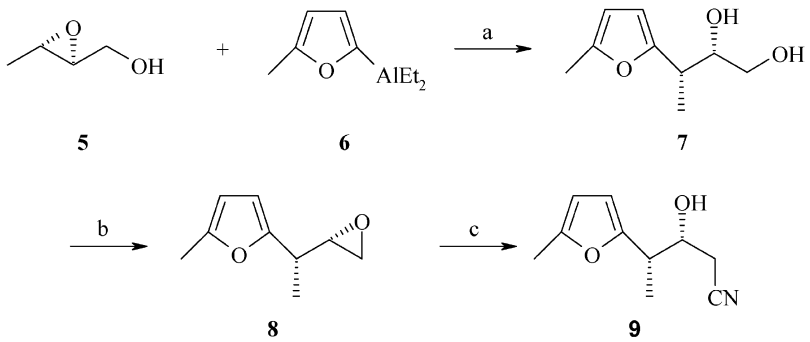
Towards this aim, the epoxide **5** (70% yield, 90% ee)[5] was treated with the aluminum derivative of 2-methylfuran **6**, readily obtained via treatment of lithium derivative with diethylaluminum chloride, to give the diol **7** with 82% yield and high 94:6 stereoselectivity.[6] Attempts to perform this condensation with a lithium derivative or by copper(I) promoted methods were unsuccessful, only traces of desired



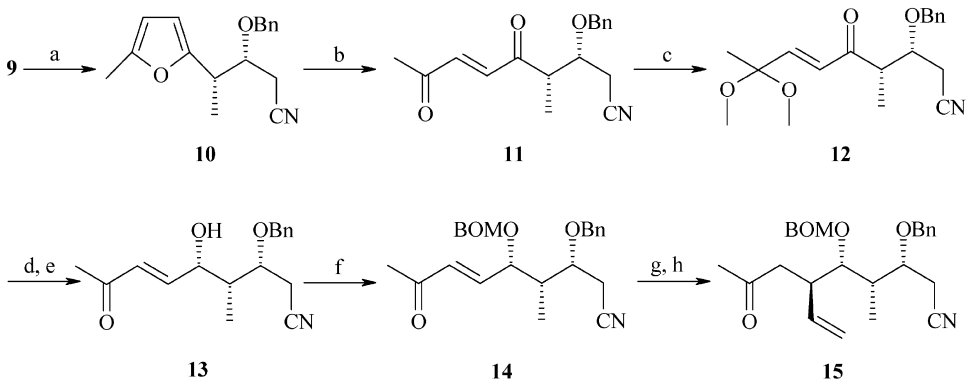
Scheme 1.

Keywords: furan ring; stereoselective synthesis; tylonolide; acyclic stereocontrol.
* Tel.: 48226326335; fax: 48226324513; e-mail: raczko@icho.edu.pl

0040–4020/$ - see front matter © 2003 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2003.10.071



Scheme 2. *Reagents and conditions*: (a) Et_2O, 0°C→RT, 16 h, 82% (b) NaH, *N*-Ts-imidazole, THF, 0°C→RT, 1.5 h, 70% (c) KCN, MeOH, reflux 3 h, 96%.



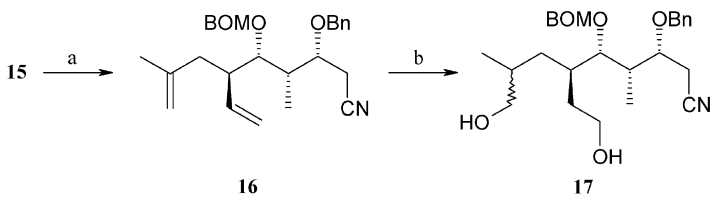
Scheme 3. *Reagents and conditions*: (a) NaH, BnBr, Bu_4NI, THF, 0°C→RT, 5 h, 90% (b) Br_2, MeCN–H_2O, −10°C→RT, 2 h, 85% (c) $CH_3C(OCH_3)_3$, camphorsulfonic acid, MeOH, RT, 3 h, 84% (d) K-selectride, THF, −100°C, 0.5 h (e) camphorsulfonic acid, acetone, RT, 0.5 h, 78% (f) BOMCl, *i*-Pr_2NEt, CH_2Cl_2, reflux 6 h, 76% (g) $CH_2CHMgBr$, CuBr·Me_2S, TMSCl, HMPA, THF, −78°C, 1 h (h) camphorsulfonic acid, MeOH, RT, 0.5 h, 80%.

product were formed. We have also observed the condensation products of furan metallated in 3- and 4-positions (less than 5%). Diol **7** was then transformed into terminal epoxide **8** in 70% yield by modified Fraser–Reid procedure,[7] followed by C-1 elongation using potassium cyanide (96% yield, Scheme 2).

The resulting alcohol **9** was benzylated (90% yield) and converted into acyclic enedione **11** by oxidation of the furan ring with Br_2/MeCN/H_2O system in 85% yield.[8] Stereoselective reduction of the C-5 carbonyl group required the regioselective protection of carbonyl C-8, executed in 84% yield by simple *trans*-ketalization with a slight excess of trimethyl ortoacetate. The best 1,3-*syn* stereoselectivity in the reduction step was achieved using potassium di-*sec*-butylborohydride (K-Selectride) at −100°C.[9] After deprotection of the 'terminal' carbonyl group we obtained the alcohol **13** in 78% overall yield and 9:1 stereoselectivity as a mixture of diastereoisomers.

A few years ago we reported a novel TMSCl and copper(I)-promoted stereoselective conjugated addition of Grignard reagents to α,β-unsaturated ketones which required a protection of the neighbouring hydroxyl with the chelating group benzyloxymethylene ether (BOM).[10] The same method was applied for introduction of the C-6 stereogenic centre. Protection of the alcohol **13** with benzyloxymethylene chloride was performed in 76% yield to give α,β-unsaturated ketone **14**. At this stage, diastereoisomers formed in reduction step were separated by column chromatography. Conjugate addition of vinylmagnesium bromide afforded, after desilylation of the resulting enol ether, ketone **15** in 80% yield and 95:5 stereoselectivity (Scheme 3).

In a final step, for introduction of C-8 stereogenic center, we applied hydroboration of the terminal olefin **16** in a process proceeding simultaneously with hydroboration of the C-6 vinyl substituent (Scheme 4). Compound **16** was obtained by olefination of the carbonyl group with methylenetriphenylphosphorane in 51% yield. Unfortunately, this olefin appeared to be very resistant to most of the known hydroborating agents.[11] Application of catechol-borane, isopinocamphenylborane or thexylborane gave none of the



Scheme 4. *Reagents and conditions*: (a) BuLi, CH_3PPh_3I, benzene, RT, 3 h, 51% (b) BH_3·THF, 0°C, THF, 3 h, 60%.

expected products. Fortunately, hydroboration with BF_3·THF provided the diol **17** in 60% yield as an inseparable 3:1 mixture of diastereoisomers at C-8 center.

In conclusion, the furan-approach turned to be a very convenient way for construction of acyclic fragments bearing five consecutive asymmetric centers. As an example we have synthesized C-1–C-9 fragment of tylonolide by stereoselective functionalization of furan-originated acyclic enedione **11** derived from 2-methylfuran. All new products were fully characterized. Configuration of newly created asymmetric centers was assigned on the bases of literature evidences.

1. Experimental

1.1. General

^1H and ^{13}C NMR spectra were recorded on a Bruker AM-500 (500 and 125 MHz) and Varian Gemini (200 and 50 MHz). Chemical shifts are reported in ppm (δ) referenced to TMS, coupling constants are measured in Hz. Mass spectra were carried out using an AMD-604 Intectra instrument. Optical rotations were measured on a JASCO DIP-360 polarimeter. Infrared spectra were recorded on a Perkin–Elmer 1640 FT-IR. Melting points were determined with a Kofler hot stage apparatus and are uncorrected. HPLC was carried out on a Knauer system using DAD spectrophotometer for peak detection. Anhydrous solvents have been dried according to standard laboratory methods. Flash-chromatography was performed according to Still et al.[12] on silica gel (Kieselgel-60 200–400 mesh, Merck).

1.1.1. (2*S*,3*S*)-3-(5-Methyl-furan-2-yl)-butane-1,2-diol 7. To a stirred solution of 2-methylfuran (1.35 ml, 15 mmol) in dry ether (8 ml) under argon at −78°C was added *n*-butyllithium (10 mmol, 1.6 M in hexane) and the reaction mixture was left to reach RT (4 h). It was then cooled to 0°C, diethylaluminum chloride (10 mmol, 1.8 M in toluene) was added dropwise and after 30 min at 0°C the epoxide **5** (190 mg, 2.16 mmol) in ether (2 ml) was added. After 16 h stirring at RT the reaction was carefully quenched with water. The aqueous layer was extracted with ethyl acetate (3×), combined organic phases were dried ($MgSO_4$), evaporated and purified by column chromatography (CH_2Cl_2/MeOH 95:5) to give 302 mg of **7** (82% yield) as a yellow oil: $[\alpha]_D$=10.4 (*c* 3.3, $CDCl_3$); ν_{max} (film, cm^{-1}) 3406, 2970, 2882, 1746, 1721, 1454, 1377, 1069, 1020, 962, 786; δ_H (200 MHz, $CDCl_3$) 5.94 (d, $J_{3',4'}$=3.0 Hz, 1H, 3′-H), 5.87 (dq, $J_{3',4'}$=3.0 Hz, $J_{4',6'}$=0.95 Hz, 1H, 4′-H), 3.79 (ddd, $J_{1A,2}$=7.5 Hz, $J_{1B,2}$=3.3 Hz, $J_{2,3}$=6.9 Hz, 1H, 2-H), 3.59 (dd_{AB}, J_{AB}=11.4 Hz, $J_{1B,2}$=3.3 Hz, 1H, 1-H_B), 3.47 (dd_{AB}, J_{AB}=11.4 Hz, $J_{1A,2}$=7.5 Hz, 1H, 1-H_A), 2.91 (dq, $J_{2,3}$=6.9 Hz, $J_{3,4}$=7.1 Hz, 1H, 3-H), 2.57 (brs, 1H, OH), 2.39 (brs, 1H, OH), 2.25 (d, $J_{4',6'}$=0.95 Hz, 3H, 6′-H), 1.29 (d, $J_{3,4}$=7.1 Hz, 3H, 4-H); δ_C (50 MHz, $CDCl_3$) 154.9 (C-2′), 150.8 (C-5′), 106.2 (C-3′), 105.9 (C-4′), 75.0 (C-2), 64.8 (C-1), 36.5 (C-3), 14.5 (C-4), 13.5 (C-6′); *m/z* (EI) 170 (M^+), 109 ($M-C_2H_5O_2$); *m/z* (HR-EI) calculated for $C_9H_{14}O_3$ (M^+) 170.09430, found 170.094. Anal. for diacetate of **7** calculated for $C_{13}H_{18}O_5$: C, 61.40; H, 7.14. Found: C, 61.67; H, 7.39.

1.1.2. (2*S*,3*S*)-3-(5-Methyl-furan-2-yl)-1,2-epoxybutane 8. To a stirred suspension of sodium hydride (80%, 264 mg, 8.79 mmol) in anhydrous THF (20 ml) diol **7** (680 mg, 4.0 mmol) in THF (5 ml) was added dropwise at 0°C under argon atmosphere. After 5 min tosylimidazole (893 mg, 4.0 mmol) was added, the reaction mixture was allowed to reach RT (1.5 h) and quenched with water. The aqueous layer was extracted with ether (3×), combined organic phases were dried ($MgSO_4$), evaporated while kept cold (the epoxide is very volatile) and purified by column chromatography (pentane/ether 98:2) to give 426 mg of **8** (70% yield) as a colourless oil: $[\alpha]_D$=47.0 (*c* 0.6, $CHCl_3$); ν_{max} (film, cm^{-1}) 3052, 2978, 2882, 1565, 1455, 1220, 1019, 953, 908, 837, 783; δ_H (200 MHz, C_6D_6) 5.84 (d, $J_{3',4'}$=3.1 Hz, 1H, 3′-H), 5.76 (dq, $J_{3',4'}$=3.1 Hz, $J_{4',6'}$=1.0 Hz, 1H, 4′-H), 2.77 (ddd, $J_{1A,2}$=2.6 Hz, $J_{1B,2}$=3.7 Hz, $J_{2,3}$=7.3 Hz, 1H, 2-H), 2.44 (dq, $J_{2,3}$=7.3 Hz, $J_{3,4}$=7.0 Hz, 1H, 3-H), 2.39 (dd_{AB}, J_{AB}=5.2 Hz, $J_{1B,2}$=3.7 Hz, 1H, 1-H_B), 2.34 (dd_{AB}, J_{AB}=5.2 Hz, $J_{1A,2}$=2.6 Hz, 1H, 1-H_A), 2.01 (d, $J_{4',6'}$=1.0 Hz, 3H, 6′-H), 1.29 (d, $J_{3,4}$=7.0 Hz, 3H, 4-H); δ_C (50 MHz, C_6D_6) 154.7 (C-5′), 150.9 (C-2′), 106.3 (C-3′), 106.0 (C-4′), 55.2 (C-2), 46.4 (C-1), 37.2 (C-3), 15.6 (C-4), 13.4 (C-6′). Anal. calculated for $C_9H_{12}O_2$: C, 71.03; H, 7.95. Found: C, 71.30; H, 8.24.

1.1.3. (3*R*,4*S*)-3-Hydroxy-4-(5-methyl-furan-2-yl)-pentanenitrile 9. The mixture of epoxide **8** (0.83 g, 5.45 mmol) and potassium cyanide (1.42 g, 21.80 mmol) in methanol (20 ml) was stirred at 80°C for 3 h. Methanol was evaporated, the residue dissolved in ethyl acetate, washed with brine and dried with $MgSO_4$. Column chromatography (CH_2Cl_2/MeOH 99:1) gave 938 mg (96% yield) of the product as a colourless oil: $[\alpha]_D$=47.0 (*c* 0.6, $CHCl_3$); ν_{max} (film, cm^{-1}) 3453, 2977, 2924, 2254, 1614, 1567, 1455, 1414, 1219, 1062, 1020, 939, 787; δ_H (200 MHz, $CDCl_3$) 6.01 (d, $J_{3',4'}$=3.1 Hz, 1H, 3′-H), 5.89 (dq, $J_{3',4'}$=3.1 Hz, $J_{4',6'}$=1.0 Hz, 1H, 4′-H), 4.05 (m, 1H, 3-H), 2.99 (dq, $J_{3,4}$=6.8 Hz, $J_{4,5}$=7.1 Hz, 1H, 4-H), 2.59 (brs, 1H, OH), 2.52 (dd_{AB}, J_{AB}=16.8 Hz, $J_{2B,3}$=4.7 Hz, 1H, 2-H_B), 2.40 (dd_{AB}, J_{AB}=16.8 Hz, $J_{2A,3}$=7.2 Hz, 1H, 2-H_A), 2.26 (d, $J_{4',6'}$=1.0 Hz, 3H, 6′-H), 1.31 (d, $J_{4,5}$=7.1 Hz, 3H, 5-H); δ_C (50 MHz, C_6D_6) 153.4 (C-5′), 151.3 (C-2′), 117.9 (C-1), 107.1 (C-3′), 106.0 (C-4′), 70.5 (C-3), 38.8 (C-4), 23.7 (C-2), 14.3 (C-5), 13.4 (C-6′); *m/z* (EI) 179 (M^+), 109 ($M-C_3H_4NO$); *m/z* (HR-EI) calculated for $C_{10}H_{13}NO_2$ (M^+) 179.09463, found 179.091. Anal. for acetate calculated for $C_{12}H_{15}NO_3$: C, 65.14; H, 6.84; N, 6.33. Found: C, 65.11; H, 7.08; N, 6.52.

1.1.4. (3*R*,4*S*)-3-Benzyloxy-4-(5-methyl-furan-2-yl)-pentanenitrile 10. To a stirred suspension of sodium hydride (80%, 98 mg, 3.26 mmol) in anhydrous THF (2 ml) nitrile **9** (450 mg, 2.51 mmol) in THF (3 ml) was added dropwise at 0°C under argon atmosphere. After 5 min benzyl bromide (0.36 ml, 3.0 mmol) and a catalytical amount of tetrabutylammonium iodide (ca. 5 mg) were added and the reaction mixture was stirred at RT for 5 h. Brine was added, the aqueous layer was extracted with ethyl acetate (3×), combined organic phases were dried ($MgSO_4$), evaporated and purified by column chromatography (hexane/ethyl

acetate 95:5→8:2) to give 610 mg of **10** (90% yield) as a colourless oil: $[\alpha]_D=-3.93$ (*c* 1.0, $CHCl_3$); ν_{max} (film, cm^{-1}) 3032, 2976, 2922, 2880, 2249, 1566, 1455, 1417, 1351, 1218, 1095, 1072, 1020, 939, 787, 739, 698;; δ_H (200 MHz, $CDCl_3$) 7.32–7.38 (m, 5H, Ph), 6.00 (d, $J_{3',4'}=3.0$ Hz, 1H, 3′-H), 5.88 (dq, $J_{3',4'}=3.0$ Hz, $J_{4',6'}=0.9$ Hz, 1H, 4′-H), 4.68 (d_{AB}, $J_{AB}=11.3$ Hz, 1H, CH_2Ph), 4.55 (d_{AB}, $J_{AB}=11.3$ Hz, 1H, CH_2Ph), 3.80 (ddd, $J_{2B,3}=4.6$ Hz, $J_{2A,3}=6.2$ Hz, $J_{3,4}=7.3$ Hz, 1H, 3-H), 3.06 (dq, $J_{3,4}=7.3$ Hz, $J_{4,5}=7.0$ Hz, 1H, 4-H), 2.55 (dd_{AB}, $J_{AB}=16.9$ Hz, $J_{2B,3}=4.6$ Hz, 1H, 2-H_B), 2.38 (dd_{AB}, $J_{AB}=16.9$ Hz, $J_{2A,3}=6.2$ Hz, 1H, 2-H_A), 2.25 (d, $J_{4',6'}=0.9$ Hz, 3H, 6′-H), 1.33 (d, $J_{4,5}=7.0$ Hz, 3H, 5-H); δ_C (50 MHz, $CDCl_3$) 153.5 (C-5′), 151.1 (C-2′), 137.4 (*i*-Ph), 128.2 (*o*-Ph), 128.0 (*m*,*p*-Ph), 117.7 (C-1), 107.1 (C-3′), 106.1 (C-4′), 77.8 (C-3), 73.0 (*C*H_2Ph), 37.8 (C-4), 21.5 (C-2), 14.9 (C-5), 13.5 (C-6′); *m*/*z* (EI) 269 (M^+), 109, 91; *m*/*z* (HR-EI) calculated for $C_{17}H_{19}NO_2$ (M^+) 269.14157, found 269.141. Anal. calculated for $C_{17}H_{19}NO_2$: C, 75.81; H, 7.11; N, 5.20. Found: C, 76.06; H, 7.05; N, 5.18.

1.1.5. (3*R*,4*S*)-3-Benzyloxy-4-methyl-5,8-dioxo-non-6-enenitrile 11. To a stirred solution of nitrile **10** (200 mg, 0.74 mmol) in 6:1 mixture of MeCN/H_2O (6 ml) bromine (154 mg, 0.96 mmol) in MeCN (2 ml) was added dropwise at −10°C and the reaction mixture was stirred at −10°C for 15 min. The cooling bath was removed and the reaction was stirred at RT for 2 h to complete *cis*/*trans* isomerization (TLC, hexane/ethyl acetate 6:4). Brine was added, the aqueous layer was extracted with ethyl acetate (3×), combined organic phases were dried ($MgSO_4$), evaporated and purified by column chromatography (hexane/ethyl acetate 7:3) to give 180 mg of **11** (85% yield) as a yellow solid mp. 59–61°C (hexane/ether); $[\alpha]_D=5.15$ (*c* 1.6, $CHCl_3$); ν_{max} (film, cm^{-1}) 3037, 2967, 2899, 2247, 1674, 1458, 1423, 1359, 1298, 1270, 1103, 1049, 996, 743, 700, 591, 477; δ_H (200 MHz, $CDCl_3$) 7.35 (s, 5H, Ph), 6.88 (s, 2H, H-6, H-7), 4.73 (d_{AB}, $J_{AB}=11.4$ Hz, 1H, CH_2Ph), 4.55 (d_{AB}, $J_{AB}=11.4$ Hz, 1H, CH_2Ph), 3.97 (ddd, $J_{2B,3}=4.8$ Hz, $J_{2A,3}=5.6$ Hz, $J_{3,4}=6.8$ Hz, 1H, 3-H), 3.22 (dq, $J_{3,4}=6.8$ Hz, $J_{4,Me}=7.1$ Hz, 1H, 4-H), 2.68 (dd_{AB}, $J_{AB}=17.1$ Hz, $J_{2B,3}=4.8$ Hz, 1H, 2-H_B), 2.55 (dd_{AB}, $J_{AB}=17.1$ Hz, $J_{2A,3}=5.6$ Hz, 1H, 2-H_A), 2.34 (s, 3H, H-9), 1.26 (d, $J_{4,Me}=7.1$ Hz, 3H, 4-Me); δ_C (50 MHz, $CDCl_3$) 201.2 (C-8), 197.7 (C-5), 137.6 (C-7), 136.8 (*i*-Ph), 135.5 (C-6), 128.6 (*o*-Ph), 128.3 (*p*-Ph), 128.1 (*m*-Ph), 117.1 (C-1), 75.0 (C-3), 72.9 (*C*H_2Ph), 48.7 (C-4), 28.5 (C-9), 20.9 (C-2), 12.8 (4-Me); *m*/*z* (EI) 286 (M+H); *m*/*z* (HR-EI) calculated for $C_{17}H_{20}NO_3$ (M+H) 286.14408, found 286.144. Anal. calculated for $C_{17}H_{19}NO_3$: C, 71.56; H, 6.71; N, 4.91. Found: C, 71.31; H, 6.73; N, 4.97.

1.1.6. (3*R*,4*S*)-3-Benzyloxy-8,8-dimethoxy-4-methyl-5-oxo-non-6-enenitrile 12. To a stirred solution of nitrile **11** (930 mg, 3.26 mmol) in anhydrous methanol (35 ml) trimethyl orthoacetate (0.42 ml, 3.30 mmol) and camphorsulfonic acid monohydrate (25 mg, 0.10 mmol) were added. The reaction mixture was stirred at RT for 3 h and quenched by addition of triethylamine (0.1 ml), then brine was added, the aqueous layer was extracted with ethyl acetate (3×), combined organic phases were dried ($MgSO_4$), evaporated and purified by column chromatography (hexane/ethyl acetate 9:1→8:2) to give 904 mg of **12** (84% yield) as a colourless oil; $[\alpha]_D=4.0$ (*c* 1.2, $CHCl_3$); ν_{max} (film, cm^{-1}) 2991, 2942, 2832, 2249, 1694, 1668, 1637, 1455, 1372, 1265, 1140, 1100, 1044, 986, 873, 745, 698; δ_H (200 MHz, $CDCl_3$) 7.30–7.40 (m, 5H, Ph), 6.68 (d_{AB}, $J_{AB}=15.8$ Hz, 1H, H-6), 6.49 (d_{AB}, $J_{AB}=15.8$ Hz, 1H, H-7), 4.72 (d_{AB}, $J_{AB}=11.3$ Hz, 1H, CH_2Ph), 4.56 (d_{AB}, $J_{AB}=11.3$ Hz, 1H, CH_2Ph), 3.94 (ddd, $J_{2B,3}=4.5$ Hz, $J_{2A,3}=5.4$ Hz, $J_{3,4}=7.5$ Hz, 1H, 3-H), 3.18 (s, 6H, 2×OMe), 3.14 ((dq, $J_{3,4}=7.5$ Hz, $J_{4,Me}=7.1$ Hz, 1H, 4-H), 2.67 (dd_{AB}, $J_{AB}=17.1$ Hz, $J_{2B,3}=4.5$ Hz, 1H, 2-H_B), 2.52 (dd_{AB}, $J_{AB}=17.1$ Hz, $J_{2A,3}=5.4$ Hz, 1H, 2-H_A), 1.39 (s, 3H, H-9), 1.25 (d, $J_{4,Me}=7.1$ Hz, 3H, 4-Me); δ_C (50 MHz, $CDCl_3$) 201.2 (C-5), 147.1 (C-6), 137.1 (*i*-Ph), 129.4 (C-7), 128.5 (*o*-Ph), 128.1 (*p*-Ph), 128.0 (*m*-Ph), 117.3 (C-1), 99.3 (C-8), 75.4 (C-3), 72.9 (*C*H_2Ph), 49.2 (2×O*Me*), 48.3 (C-4), 23.0 (C-9), 21.2 (C-2), 13.6 (4-Me); *m*/*z* (EI) 331 (M^+), 316 ($M-CH_3$), 300 ($M-OCH_3$); *m*/*z* (HR-EI) calculated for $C_{18}H_{22}NO_3$ ($M-OCH_3$) 300.15952, found: 300.159.

1.1.7. (3*R*,4*S*,5*S*)-3-Benzyloxy-5-hydroxy-4-methyl-8-oxo-non-6-ene-nitrile 13. To a stirred solution of dimethoxynitrile **12** (740 mg, 2.23 mmol) in anhydrous THF (25 ml) potassium tri-*sec*-butylborohydride (2.8 ml, 1 M in THF) was added dropwise at −100°C (liquid nitrogen, ether). The reaction mixture was stirred for 30 min and excess of borohydride was quenched with MeOH (1 ml). H_2O_2 (20%, 1 ml) and NaOH (30%, 1 ml) were added and the reaction mixture was stirred at RT for 15 min. After addition of brine the aqueous layer was extracted with ethyl acetate (3×), combined organic phases were evaporated and redissolved in acetone (15 ml). Camphorosulfonic acid monohydrate (20 mg) was added and the mixture was stirred at RT for 30 min. After addition of triethylamine (0.3 ml) and evaporation of solvents the residue was dissolved in ethyl acetate and worked up as usual. Column chromatography (hexane/ethyl acetate 8:2→6:4) gave 502 mg of **13** (78% yield) as a colourless oil (9:1 mixture of diastereoisomers). For analytical purposes the major isomer was isolated by preparative HPLC (Nucleosil-100, hexane/ethyl acetate 8:2); $[\alpha]_D=-11.7$ (*c* 1.1, $CHCl_3$); ν_{max} (film, cm^{-1}) 3459, 3032, 2927, 2249, 1676, 1630, 1455, 1421, 1360, 1257, 1099, 1059, 983, 741, 699; δ_H (200 MHz, $CDCl_3$) 7.29–7.43 (m, 5H, Ph), 6.74 (dd, $J_{6,7}=15.9$ Hz, $J_{5,6}=5.5$ Hz, 1H, H-6), 6.28 (dd, $J_{6,7}=15.9$ Hz, $J_{5,7}=1.5$ Hz, 1H, H-7), 4.73 (d_{AB}, $J_{AB}=11.4$ Hz, 1H, CH_2Ph), 4.55 (d_{AB}, $J_{AB}=11.4$ Hz, 1H, CH_2Ph), 4.21 (ddt, $J_{5,OH}=J_{5,6}=5.5$ Hz, $J_{4,5}=5.3$ Hz, $J_{5,7}=1.5$ Hz, 1H, H-5), 4.14 (dt, $J_{2A,3}=J_{2B,3}=6.6$ Hz, $J_{3,4}=2.7$ Hz, 1H, H-3), 2.73 (dd_{AB}, $J_{AB}=16.8$ Hz, $J_{2A,3}=6.5$ Hz, 1H, 2-H_A), 2.64 (d, $J_{5,OH}=5.5$ Hz, 1H, OH), 2.53 (dd_{AB}, $J_{AB}=16.8$ Hz, $J_{2B,3}=6.7$ Hz, 1H, 2-H_B), 2.26 (s, 3H, 9-H), 1.96 (ddq, $J_{3,4}=2.7$ Hz, $J_{4,5}=5.3$ Hz, $J_{4,Me}=7.1$ Hz, 1H, 4-H), 1.03 (d, $J_{4,Me}=7.1$ Hz, 3H, 4-Me); δ_C (50 MHz, $CDCl_3$) 198.1 (C-8), 147.0 (C-7), 136.8 (*i*-Ph), 130.7 (C-6), 128.7 (*m*-Ph), 128.4 (*p*-Ph), 128.1 (*o*-Ph), 117.5 (C-1), 75.0 (C-3), 73.5 (C-5), 72.7 (O*C*H_2Ph), 41.6 (C-4), 27.6 (C-9), 20.4 (C-2), 10.6 (4-Me); *m*/*z* (LSIMS) 310 (M+Na), 288 (M+H); *m*/*z* (HR-LSIMS) calculated for $C_{17}H_{21}NO_3Na$: 310.13983, found: 310.140. Anal. calculated for $C_{17}H_{21}NO_3$: C, 71.06; H, 7.37; N, 4.87. Found: C, 70.82; H, 7.45; N, 4.99.

1.1.8. (3*R*,4*S*,5*S*)-3-Benzyloxy-5-benzyloxymethoxy-4-methyl-8-oxo-non-6-ene-nitrile 14. To a stirred diastereomeric mixture of alcohol **13** (338 mg, 1.18 mmol)

and *N*-ethyldiisopropylamine (1 ml, 5.74 mmol) in dry CH_2Cl_2 (10 ml) benzyl chloromethyl ether (60%, 1 ml, 4.31 mmol) was added under argon atmosphere. The reaction was refluxed for 6 h, poured into brine, extracted with ethyl acetate (3×) and dried over anhydrous $MgSO_4$. Column chromatography (hexane/ethyl acetate 8:2→6:4) gave 365 mg (76% yield) of the pure diastereoisomer. Colourless oil: $[\alpha]_D=-25.3$ (*c* 0.68, $CHCl_3$); ν_{max} (film, cm^{-1}) 2921, 1672, 1630, 1451, 1356, 1254, 1097, 1027, 986, 738, 697; δ_H (200 MHz, $CDCl_3$) 7.22–7.36 (m, 10H, 2×Ph), 6.60 (dd, $J_{6,7}=16.1$ Hz, $J_{5,6}=7.7$ Hz, 1H, 6-H), 6.17 (dd, $J_{6,7}=16.1$ Hz, 1H, 7-H), 4.70 (d_{AB}, $J_{AB}=6.9$ Hz, 1H, OCH_2OBn), 4.68 (d_{AB}, $J_{AB}=11.4$ Hz, 1H, OCH_2Ph), 4.64 (d_{AB}, $J_{AB}=6.9$ Hz, 1H, OCH_2OBn), 4.62 (d_{AB}, $J_{AB}=11.9$ Hz, 1H, OCH_2OCH_2Ph), 4.56 (d_{AB}, $J_{AB}=11.9$ Hz, 1H, OCH_2OCH_2Ph), 4.50 (d_{AB}, $J_{AB}=11.4$ Hz, 1H, OCH_2Ph), 4.09–4.20 (m, 2H, 3-H, 5-H), 2.70 (dd_{AB}, $J_{AB}=16.9$ Hz, $J_{2A,3}=6.3$ Hz, 1H, 2-H_A), 2.53 (dd_{AB}, $J_{AB}=16.9$ Hz, $J_{2B,3}=6.8$ Hz, 1H, 2-H_B), 2.17 (s, 3H, 9-H), 1.90–2.08 (m, 1H, 4-H), 0.94 (d, $J_{4,Me}=7.1$ Hz, 3H, 4-Me); δ_C (50 MHz, $CDCl_3$) 197.9 (C-8), 144.8 (C-7), 137.5 (*i*-Ph), 137.3 (*i*-Ph), 132.6 (C-6), 128.5, 127.9, 127.8, 127.6, 127.5 (2×Ph), 117.7 (C-1), 93.4 (OCH_2OBn), 78.5 (C-5), 74.3 (C-3), 72.6 (OCH_2Ph), 70.1 (OCH_2OCH_2Ph), 41.8 (C-4), 27.2 (C-9), 21.1 (C-2), 9.9 (4-Me); *m/z* (LSIMS) 430 (M+Na), 408 (M+H); *m/z* (HR-LSIMS) calculated for $C_{25}H_{29}NO_4Na$: 430.19973, found: 430.199. Anal. calculated for $C_{25}H_{29}NO_4$: C, 73.68; H, 7.17; N, 3.44. Found: C, 73.42, H, 7.08, N, 3.32.

1.1.9. (3*R*,4*S*,5*S*,6*R*)-3-Benzyloxy-5-benzyloxymethoxy-4-methyl-6-(2-oxo-propyl)-oct-7-ene-nitrile 15. To a suspension of $CuBr{\cdot}Me_2S$ (26 mg, 0.12 mmol) and dry HMPA (0.145 ml, 0.83 mmol) in dry THF (5 ml), under argon atmosphere at −78°C was added a solution of vinylmagnesium bromide (1.25 ml, 1 M in THF) and stirred for 10 min. To this mixture was added a precooled solution of **14** (170 mg, 0.42 mmol) and TMSCl (0.08 ml, 0.63 mmol) in THF (2 ml). The reaction was stirred at −78°C for 1 h, aqueous NH_4Cl was added to the mixture, which was then extracted with ethyl acetate (3×) and evaporated under reduced pressure. The residue was dissolved in MeOH (6 ml), a catalytic amount of camphorsulfonic acid (ca. 10 mg) was added and the reaction mixture was stirred at RT for 30 min. Then, brine was added, the aqueous layer was extracted with ethyl acetate (3×), combined organic phases were dried ($MgSO_4$), evaporated and purified by column chromatography (hexane/ethyl acetate 9:1) to give 146 mg of **15** (80% yield) as a colourless oil; $[\alpha]_D=-20.5$ (*c* 1.6, $CHCl_3$); ν_{max} (film, cm^{-1}) 3065, 2922, 2248, 1714, 1497, 1454, 1358, 1096, 1027, 924, 738, 699; δ_H (200 MHz, $CDCl_3$) 7.23–7.37 (m, 10H, 2×Ph), 5.78 (ddd, $J_{6,7}=10.0$ Hz, $J_{7,8A}=7.9$ Hz, $J_{7,8B}=17.7$ Hz, 1H, 7-H), 5.08–5.13 (m, 1H, 8-H_A), 5.0–5.05 (m, 1H, 8-H_B), 4.74 (d_{AB}, $J_{AB}=6.7$ Hz, 1H, OCH_2OBn), 4.70 (d_{AB}, $J_{AB}=6.7$ Hz, 1H, OCH_2OBn), 4.67 (d_{AB}, $J_{AB}=11.8$ Hz, 1H, OCH_2OCH_2Ph), 4.59 (d_{AB}, $J_{AB}=11.8$ Hz, 1H, OCH_2OCH_2Ph), 4.54 (d_{AB}, $J_{AB}=11.5$, 1H, OCH_2Ph), 4.46 (d_{AB}, $J_{AB}=11.5$ Hz, 1H, OCH_2Ph), 4.12 (ddd, $J_{2A,3}=5.8$ Hz, $J_{2B,3}=7.1$ Hz, $J_{3,4}=2.7$ Hz, 1H, 3-H), 3.53 (dd, $J_{4,5}=7.7$ Hz, $J_{5,6}=3.8$ Hz, 1H, 5-H), 2.87–3.02 (m, 1H, 6-H), 2.64 (dd_{AB}, $J_{AB}=16.8$ Hz, $J_{2A,3}=5.8$ Hz, 1H, 2-H_A), 2.49 (dd_{AB}, $J_{AB}=16.8$ Hz, $J_{2B,3}=7.1$ Hz, 1H, 2-H_B), 2.44–2.71 (m, 2H, CH_2COMe), 2.13 (s,3H, CH_2COMe), 1.78–1.95 (m, 1H, 4-H), 0.98 (d, $J_{4,Me}=7.1$ Hz, 3H, 4-Me); δ_C (50 MHz, $CDCl_3$) 207.4 (C=O), 139.0 (C-7), 137.7 (*i*-Ph), 137.5 (*i*-Ph), 128.4, 127.9, 127.8, 127.7, 127.6, 127.4 (2×Ph), 117.9 (C-1), 116.6 (C-8), 96.8 (OCH_2OBn), 84.5 (C-5), 74.4 (C-3), 72.1 (OCH_2Ph), 70.3 (OCH_2OCH_2Ph), 42.6 (CH_2COMe), 41.5 (C-4), 40.3 (C-6), 30.6 (CH_2COMe), 21.1 (C-2), 10.6 (4-Me); *m/z* (LSIMS) 458 (M+Na), 436 (M+H); *m/z* (HR-LSIMS) calculated for $C_{27}H_{33}NO_4Na$: 458.23072, found: 458.230. Anal. calculated for $C_{27}H_{33}NO_4$: C, 74.45; H, 7.64; N, 3.22. Found: C, 74.34, H, 7.55, N, 2.80.

1.1.10. (3*R*,4*S*,5*S*,6*R*)-3-Benzyloxy-5-benzyloxymethoxy-4-methyl-6-vinyl-8-methyl-non-8-ene-nitrile 16. To a solution of methyltriphenylphosphonium iodide (280 mg, 0.69 mmol) in dry benzene (5 ml), under argon atmosphere at RT was added *n*-butyllithium (0.44 ml, 1.6 M in hexane). The resulting mixture was stirred for 1 h and then the ketone **15** (151 mg, 0.35 mmol) in benzene (3 ml) was slowly added. The reaction mixture was stirred at RT for 3 h, quenched by addition of brine, extracted with ethyl acetate (3×), dried with $MgSO_4$, evaporated and purified by column chromatography (hexane/ethyl acetate 9:1→8:2) to give 77 mg of **16** (51% yield) as a colourless oil, 48 mg (32%) of the substrate was recovered; $[\alpha]_D=-12.3$ (*c* 1.1, $CHCl_3$); ν_{max} (film, cm^{-1}) 3082, 2916, 2258, 1492, 1462, 1348, 1098, 1015, 922, 740, 703; δ_H (200 MHz, $CDCl_3$) 7.24–7.37 (m, 10H, 2×Ph), 5.73 (ddd, $J=9.5$ Hz, $J=8.4$ Hz, $J=17.9$ Hz, 1H, $CH=CH_2$), 5.07–5.11 (m, 1H, $CH=CH_2$), 4.99–5.05 (m, 1H, $CH=CH_2$), 4.76 (d_{AB}, $J_{AB}=6.7$ Hz, 1H, OCH_2OBn), 4.72 (d_{AB}, $J_{AB}=6.7$ Hz, 1H, OCH_2OBn), 4.69 (d_{AB}, $J_{AB}=11.9$ Hz, 1H, OCH_2OCH_2Ph), 4.61 (d_{AB}, $J_{AB}=11.9$ Hz, 1H, OCH_2OCH_2Ph), 4.61–4.70 (m, 2H, $C=CH_2$), 4.56 (d_{AB}, $J_{AB}=11.3$ Hz, 1H, OCH_2Ph), 4.48 (d_{AB}, $J_{AB}=11.3$ Hz, 1H, OCH_2Ph), 4.17 (ddd, $J_{2A,3}=6.0$ Hz, $J_{2B,3}=6.9$ Hz, $J_{3,4}=2.5$ Hz, 1H, 3-H), 3.53 (dd, $J_{4,5}=7.9$ Hz, $J_{5,6}=3.4$ Hz, 1H, 5-H), 2.68 (dd_{AB}, $J_{AB}=16.8$ Hz, $J_{2A,3}=6.0$ Hz, 1H, 2-H_A), 2.49 (dd_{AB}, $J_{AB}=16.8$ Hz, $J_{2B,3}=6.9$ Hz, 1H, 2-H_B), 2.44–2.61 (m, 1H, 6-H), 2.25 (dd_{AB}, $J_{AB}=14.5$ Hz, $J_{6,7A}=4.6$ Hz, 1H, 7-H_A), 2.13 (dd_{AB}, $J_{AB}=14.5$ Hz, $J_{6,7B}=10.4$ Hz, 1H, 7-H_B), 1.80–2.03 (m, 1H, 4-H), 1.68 (s, 3H, 8-Me), 1.00 (d, $J=7.1$ Hz, 3H, 4-Me); δ_C (50 MHz, $CDCl_3$) 143.6 (C-8), 139.9 (*C*H-vinyl), 138.0 (*i*-Ph), 137.6 (*i*-Ph), 128.4, 128.3, 127.8, 127.7, 127.6, 127.5 (2×Ph), 118.0 (C-1), 116.2 (CH_2-vinyl), 112.0 ($C=CH_2$), 96.8 (OCH_2OBn), 85.3 (C-5), 74.5 (C-3), 72.2 (OCH_2Ph), 70.3 (OCH_2OCH_2Ph), 44.2 (C-6), 40.2 (C-4), 36.5 (C-7), 22.3 (9-Me) 21.3 (C-2), 10.7 (4-Me); *m/z* (LSIMS) 456 (M+Na), 434 (M+H); *m/z* (HR-LSIMS) calculated for $C_{28}H_{35}NO_3Na$: 456.25947, found: 456.259.

1.1.11. (3*R*,4*S*,5*S*,6*R*)-3-Benzyloxy-5-benzyloxymethoxy-4,8-dimethyl-9-hydroxy-6-(2-hydroxy-ethyl)-nonane-nitrile 17. To a solution of **16** (40 mg, 0.092 mmol) in dry THF (5 ml) was added borane-THF complex (1.5 ml, 1.0 M in THF) at 0°C. The reaction mixture was stirred for 3 h at 0°C and quenched with H_2O_2 (0.5 ml) and NaOH (0.5 ml). Brine was then added and the product was extracted with Et_2O (3×), dried and purified by column chromatography (hexane/ethyl acetate 7:3→1:1) to give 26 mg of **17** (60% yield) as a colorless oil (ca. 3:1 mixture of diastereoisomers); δ_H (500 MHz, $CDCl_3$, major isomer) 7.27–7.36 (m, 10H, 2×Ph), 4.78 (d_{AB}, $J_{AB}=6.8$ Hz, 1H, OCH_2OBn),

4.75 (d_{AB}, J_{AB}=6.8 Hz, 1H, OCH_2OBn), 4.51–4.69 (m, 4H, OCH_2Ph x 2), 4.24 (ddd_{AB}, J_{AB}=10.9 Hz, J=5.7 Hz, J=0.6 Hz, 1H, 9-H_A), 4.20 (ddd_{AB}, J_{AB}=10.9 Hz, J=6.1 Hz, J=0.6 Hz, 1H, 9-H_B), 4.07 (ddd, $J_{2A,3}$=7.0 Hz, $J_{2B,3}$=5.7 Hz, $J_{3,4}$=2.8 Hz, 1H, 3-H), 3.99 (dd, $J_{4,5}$=6.3 Hz, $J_{5,6}$=4.0 Hz, 1H, 5-H), 3.53–3.70 (m, 2H, CH_2OH), 3.41–3.52 (m, 2H, 2×OH), 2.70 (dd_{AB}, J_{AB}=16.8 Hz, $J_{2B,3}$=5.7 Hz, 1H, 2-H_B), 2.57 (dd_{AB}, J_{AB}=16.8 Hz, $J_{2A,3}$=7.0 Hz, 1H, 2-H_A), 1.87–2.07 (m, 1H, 4-H), 1.59–1.79 (m, 2H, 7-CH_2), 1.35–1.47 (m, 1H, 6-H), 1.15–1.27 (m, 3H, C_6–CH_2, 8-H), 1.00 (d, J=7.0 Hz, 3H, Me), 0.93 (d, J=6.7 Hz, 3H, Me); δ_C (125 MHz, $CDCl_3$) 137.7 (*i*-Ph), 137.3 (*i*-Ph), 128.8, 128.5, 128.6, 127.8, 127.7, 127.4 (2×Ph), 118.1 (C-1), 96.8 (O*C*H_2OBn), 84.8 (C-5), 74.6 (C-3), 71.7 (O*C*H_2Ph), 70.4 (OCH_2O*C*H_2Ph), 40.9 (C-4), 28.9, 28.3 (2×*C*H_2OH), 23.7 (C-7), 22.9 (C-2), 21.9 (C-6), 21.1 (6-*C*H_2), 17.4 (C-8), 14.0 (8-Me), 10.9 (4-Me); *m/z* (LSIMS) 492 (M+Na); *m/z* (HR-LSIMS) calculated for $C_{28}H_{39}NO_5Na$: 492.26461, found: 492.264.

References

1. (a) Boeckman, R. K.; Goldstein, S. W. *The Total Synthesis of Natural Products*; Ap-Simon, J., Ed.; Wiley: New York, 1988; Vol. 8, pp 1–140. (b) Paterson, I.; Mansuri, M. *Tetrahedron* **1985**, *41*, 3569. (c) Kirst, H. A. In *Recent Progress in the Synthesis of Antibiotics*; Lukacs, G., Ohno, M., Eds.; Springer: Berlin, 1990; p 39.
2. (a) Tatsuta, K.; Amemiya, Y.; Kanemura, Y.; Kinoshita, M. *Tetrahedron Lett.* **1981**, *22*, 3397. (b) Nicolaou, K. C.; Pavia, M. R.; Seitz, S. P. *J. Am. Chem. Soc.* **1982**, *104*, 2027. (c) Grieco, P. A.; Inanaga, J.; Lin, N.-H.; Yanami, T. *J. Am. Chem. Soc.* **1982**, *104*, 5781. (d) Masamune, S.; Kaiko, T.; Garvey, D. S. *J. Am. Chem. Soc.* **1982**, *5521*, 5523. (e) Evans, D. A. *Aldrichimica Acta* **1982**, *15*, 23. (f) Tanaka, T.; Oikawa, Y.; Hamada, T.; Yonemitsu, O. *Chem. Pharm. Bull.* **1987**, *35*, 2209.
3. Syntheses of fragments of tylonolide: (a) Lu, L. D.-L. *Tetrahedron Lett.* **1982**, *23*, 1867. (b) Kitano, Y.; Kusakabe, M.; Kobayashi, Y.; Sato, F. *Chem. Lett.* **1986**, 523. (c) Pearson, A. J.; Lai, Y.-S.; Lu, W.; Pinkerton, A. A. *J. Org. Chem.* **1989**, *54*, 3882. (d) Hughes, A. B.; Stick, R. V.; Tilbrook, D. M. G. *Aust. J. Chem.* **1990**, *43*, 1681. (e) Guanti, G.; Banfi, L.; Ghiron, C.; Narisano, E. *Tetrahedron Lett.* **1991**, *32*, 267. (f) Marshall, J. A.; Yashunsky, D. V. *J. Org. Chem.* **1991**, *56*, 5493. (g) Marshall, J. A.; Crute, III, T. D.; His, J. D. *J. Org. Chem.* **1992**, *57*, 115. (h) Le Ménez, P.; Fargeas, V.; Berque, I.; Poisson, J.; Ardisson, J.; Lallemand, J.-Y.; Pancrazi, A. *J. Org. Chem.* **1995**, *60*, 3592. (i) Berque, I.; Le Ménez, P.; Razon, P.; Pancrazi, A.; Ardisson, J.; Brion, J. D. *Synlett* **1998**, 1135.
4. (a) Pikul, S.; Raczko, J.; Ankner, K.; Jurczak, J. *J. Am. Chem. Soc.* **1987**, *109*, 3981. (b) Raczko, J.; Jurczak, J. *Studies in Natural Products Synthesis*; Atta-ur-Rahman, Ed.; Elsevier: Amsterdam, 1995; Vol. 16, p 639. (c) Raczko, J. *Polish J. Chem.* **1999**, *73*, 77.
5. Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974.
6. Suzuki, T.; Saimoto, H.; Tomioka, H.; Oshima, K.; Nozaki, H. *Tetrahedron Lett.* **1982**, *23*, 3597.
7. Hicks, D. R.; Fraser-Reid, B. *Synthesis* **1974**, 203.
8. Jurczak, J.; Pikul, S. *Tetrahedron Lett.* **1985**, *26*, 3039.
9. (a) Narasaka, K.; Pai, F.-C. *Tetrahedron* **1984**, *40*, 2233. (b) Evans, D. A.; Dart, M. J.; Duffy, J. L. *Tetrahedron Lett.* **1994**, *35*, 8541. (c) Mori, Y.; Kuhara, M.; Takeuchi, A.; Suzuki, M. *Tetrahedron Lett.* **1988**, *29*, 5419.
10. Raczko, J. *Tetrahedron: Asymmetry* **1997**, *8*, 3821.
11. Zaidlewicz, M. *Houben-Weyl Methods of Organic Chemistry*; Georg Thieme: New York, 1995; Vol. E21e. pp 4519–4530.
12. Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2939.