Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron 60 (2004) 9199–9204
Tetrahedron

An expedient synthesis of spiroketals: model studies for the calyculin C_{16}–C_{25} fragment

Vesa Rauhala, Marta Nevalainen and Ari M. P. Koskinen*

Department of Chemical Technology, Laboratory of Organic Chemistry, Helsinki University of Technology, Kemistintie 1, P.O. Box 6100, Espoo FIN-02015 HUT, Finland

Received 28 April 2004; revised 30 June 2004; accepted 23 July 2004

Available online 27 August 2004

Abstract—A new short strategy to prepare the spiroketal fragment of calyculins is presented. A novel Seyferth–Gilbert type homologation of hindered lactols to the corresponding alkynes has been achieved for the first time. The spirocyclization was achieved efficiently via a DIHMA (double intramolecular hetero-Michael addition) process of this hindered ynone. The spirocyclization rate is not dependent on the stereochemistry of the alkoxy substituent in the oxolane ring.

1. Introduction

The 1,6-dioxaspiro[4.5]decane ring system is a common motif, occurring in nearly 100 natural products.[1] It is noteworthy that in most of these structures, the configuration of the stereogenic carbon atom is dictated by double anomeric effect, placing the oxygen in the oxolane ring axial with respect to the oxane ring (Fig. 1).[2] Due to the wide occurrence of such structures, a rapid and reliable entry into the spirocyclic structure is highly desirable. This was of special interest to us because of our ongoing efforts towards the total synthesis of calyculin C, a potent protein phosphatase inhibitor.[3,4] In this paper we report our recent results on a highly convergent strategy to achieve this goal.[5]

Our retrosynthetic strategy for the model spiroketal is based on a convergent strategy (Scheme 1). The actual spiroketal formation is based on the DIHMA (double intramolecular hetero-Michael addition) process of a suitably derived ynone.[6] Thus, our penultimate goal became the ynone **13**, which would be available through a nucleophilic addition of the alkyne **8** onto the Weinreb amide **12**, in turn available via Evans aldol methodology from propionyloxazolidinone **9** and benzyloxypropanal. The alkyne was envisioned to arise through a Seyferth–Gilbert-type homologation[7] of the aldehyde (or lactol) corresponding to lactone **4**.

Although seemingly well precedented, several questions remained to be answered. First, the electrophilic end of the ynone **13a**,**b** is highly sterically crowded, which might affect the cyclization rate. Secondly, the formation of the highly substituted alkyne **8** is not trivial. Thirdly, the existence of the requisite alkoxy group in the oxolane ring might affect the cyclization rate and/or the stability of the ensuing spirocycle. To shed light on this latter question, we decided to enter the spirocyclization with enantiopure **12** and racemic **8**. Rate differences between the diastereomers would thus become evident experimentally.

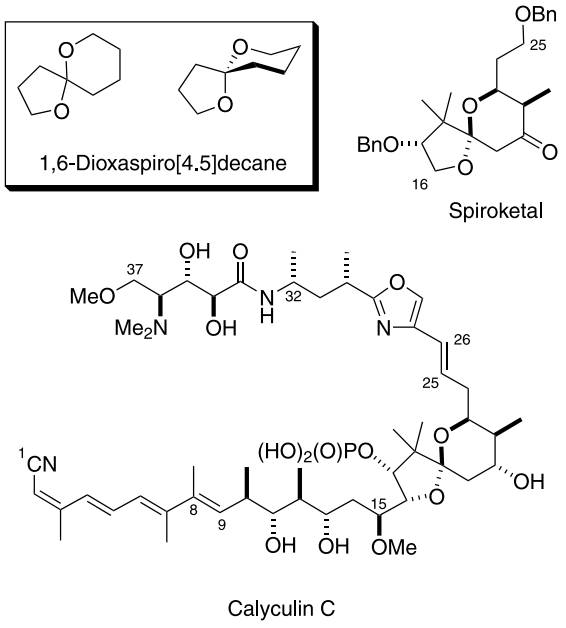
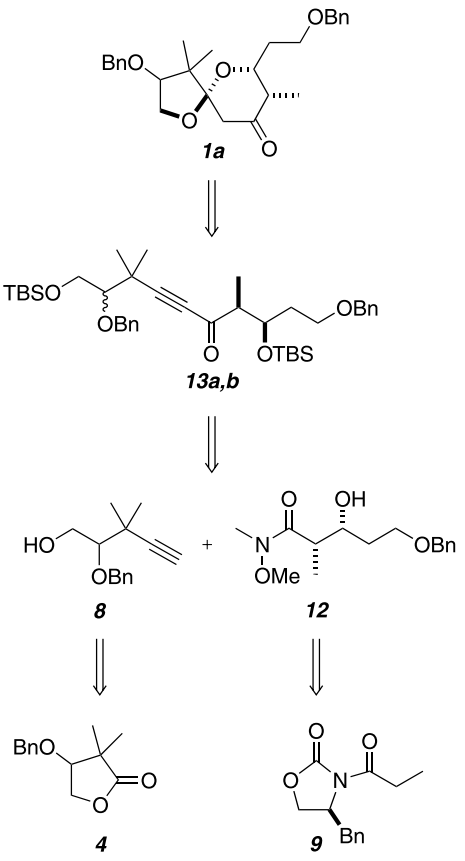


Figure 1. Spiroketal fragment of calyculin C.

Keywords: Enantioselectivity; Natural product; Spiroketals.
* Corresponding author. Tel.: +3589451-2526; fax: +3589451-2538; e-mail: ari.koskinen@hut.fi

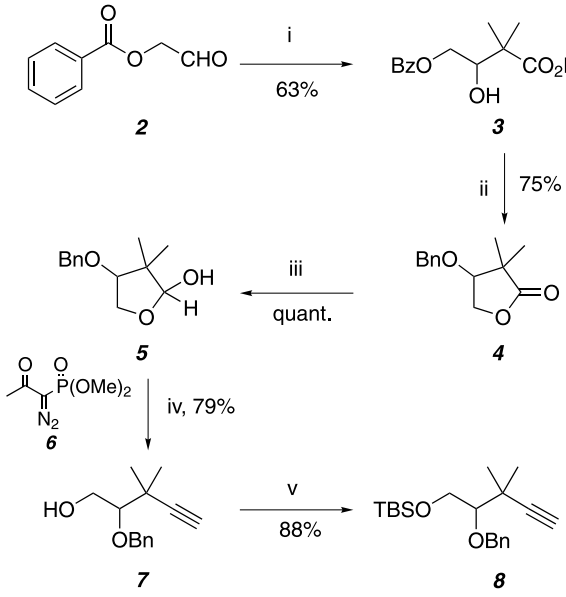
0040–4020/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2004.07.059



Scheme 1. Retrosynthetic analysis of spiroketal **1a**.

2. Results

The alkyne **8** was prepared as shown in Scheme 2, beginning with an addition of the ester enolate of ethyl isobutyrate to 2-benzoyloxyacetaldehyde **2** affording the hydroxy ester **3** in 63% yield. Protection of the hydroxy group (NaH, BnCl, 75%) and DIBAL-H reduction of the lactone gave lactol **5** in near quantitative yield, ready for the Seyferth–Gilbert type homologation to the alkyne without further purification. If the initial ester aldol reaction was allowed to warm to higher temperatures, the intermediate alkoxide corresponding to **3** further reacted, by intramolecular benzoate transfer and ring closure, to give the hydroxy lactone directly. Quenching the reaction mixture with benzyl chloride gave **4** in a one-pot operation, however, with yields typically below 25%. We therefore decided to rely on the more reproducible two step operation.

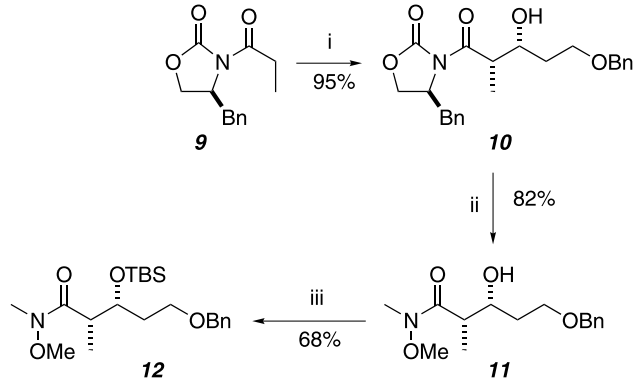


Scheme 2. Reagents: (i) LDA, Me_2CHCO_2Et, THF, −78 °C, then **2**; (ii) NaH, BnCl, DMF, THF, 0 °C; (iii) DIBAL-H, PhMe, −78 °C; (iv) **6**, K_2CO_3, MeOH, 36 °C; (v) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C.

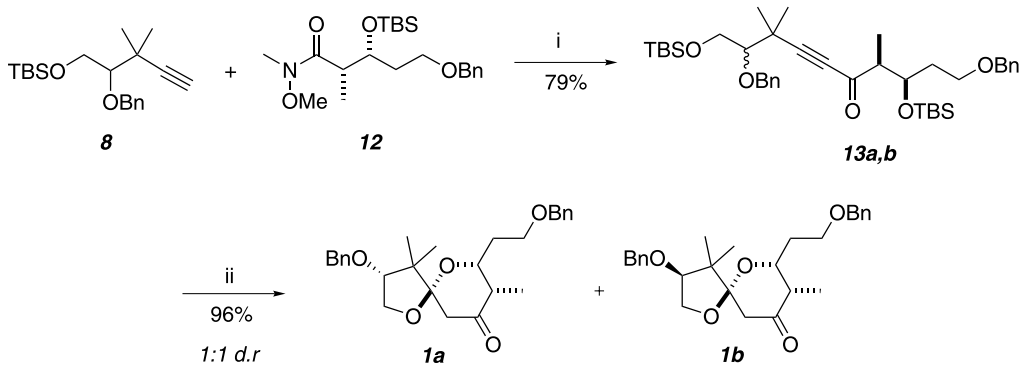
Ohira's reagent **6** is a mild alternative to the original Seyferth–Gilbert homologation, widely used to transform an aldehyde to the corresponding alkyne.[8] In our case, the lactol **5** was used as the aldehyde surrogate.[9] The relative sluggishness of the lactol for ring-chain tautomerism was evident experimentally: Ohira's reagent **6** had to be added slowly (in five ca. 50 mol% portions over 5 days), and the reaction temperature had to be kept low (between 36 and 44 °C) in order to achieve acceptable yields reproducibly (60–79%, based on recovered starting material). Higher reaction temperatures or faster addition of reagent **6** and the base led to decomposed products. This successful procedure represents the first successful example of using a hindered lactol in the Seyferth–Gilbert homologation. Finally, the secondary hydroxyl was protected (TBSOTf, lutidine, 88%) to give the alkyne **8** ready for coupling.

The enantiopure fragment, Weinreb amide **12**, was prepared using the diastereoselective Evans *syn*-aldol reaction from the known propionyloxazolidinone **9** and 3-benzyloxypropionaldehyde (Scheme 3). Thus, reaction of the dibutylboron *Z*-enolate of **9** and the aldehyde gave the desired **10** in 95% yield. Conversion of **10** to the Weinreb amide **11** (82%), followed by TBS protection under standard conditions[10] gave the coupling partner **12** (68%).

Fragments **8** and **12** were coupled using the Weinreb–Nahm procedure to produce alkynone **13a**,**b**.[11] Spirocyclization with the DIHMA procedure was then attempted using a stepwise protocol.[11] In the first step, the TBS protections were cleavage by CSA in MeOH. Some spirocyclization occurred already at this stage (TLC). Thus, the solvent was removed and replaced with benzene, and addition of *p*-TsOH took the spirocyclization to completion. Because



Scheme 3. Reagents: (i) **9**, Bu_2BOTf, Et_3N, CH_2Cl_2; then $BnOCH_2CH_2$-CHO, −77 °C; (ii) MeOMeNH·HCl, $AlMe_3$, THF, 0 °C; (iii) TBSCl, Im, DMF, 0 °C.



Scheme 4. Coupling of **8** and **12** and spirocyclization. Reagents: (i) BuLi, **8**, then **12**, THF −78 °C; (ii) CSA, MeOH, then *p*-TsOH, PhH, rt.

the alkyne **8** was not optically pure, the two diastereoisomers **1a** and **1b** were observed in a 1:1 diastereomeric ratio (Scheme 4). This supports the conclusion that the cyclization rate is not critically dependent on the existence of a directing alkoxy group in the oxolane ring.

3. Conclusions

We have presented a new strategy to prepare the spiroketal fragment of calyculins. A novel Seyferth–Gilbert type homologation of hindered lactols to the corresponding alkynes has been achieved for the first time. The spirocyclization was achieved efficiently via a DIHMA (double intramolecular hetero-Michael addition) process. The spirocyclization rate is not dependent on the stereochemistry of the alkoxy substituents in the oxolane ring. Application of this protocol in the total synthesis of calyculin C will be reported in due course.

4. Experimental

4.1. General

All reactions were conducted under a positive pressure of argon. THF was distilled prior to use from sodium-benzophenone, MeOH from $Mg(OMe)_2$ and toluene from sodium. Other solvents were pro analysis grade.

Melting points were determined on a Gallenkamp melting point apparatus MFB-595 and are uncorrected. TLC was conducted on Merck 0.25 mm silica gel 60 F plates and samples were visualized with UV light, anisaldehyde, PMA or ninhydrin staining. Flash chromatography was performed using Merck silica gel 60 (230–400 mesh) as a stationary phase. HPLC was performed with Waters 501 pump, Waters 486 tunable absorbance detector, Waters 746 data module using the following columns: Shandon Hypersil Silica Column with Waters Guard-Pak™ precolumn fitted with Resolve™ silica inserts for normal phase chromatography and Daicel Chiralcel OD 25 cm×0.46 cm with Daicel Chiracel OD 5 cm×0.46 cm precolumn for chiral chromatography. Optical rotations were measured at 20 °C on a Perkin–Elmer polarimeter 343. IR spectra were measured with Perkin–Elmer Spectrum One.

Elemental analyses were performed with Perkin–Elmer Elemental Analyzer 2400 CHN. HRMS spectra were measured with Jeol JMS-DX 303 and Micromass LCT. NMR spectra were measured with Bruker AMX 400 (^{1}H 400.13 MHz, ^{13}C 100.61 MHz).

4.1.1. 3-(Ethoxycarbonyl)-2-hydroxy-3-methylbutyl benzoate 3. Diisopropylamine (2.82 mL, 20.1 mmol, 110 mol%) was dissolved in freshly distilled THF (20 mL) at 0 °C. BuLi (2.3 M, 8.7 mL, 20.1 mmol, 110 mol%) was added during 10 min and the light yellow solution was cooled to −78 °C. Ethyl isobutyrate (2.69 mL, 20.1 mmol, 110 mol%) was added dropwise during 5 min. The light yellow reaction mixture was stirred 1.5 h at −78 °C and aldehyde **2** (3.0 g, 18.3 mmol, 100 mol%) in THF was added dropwise over 20 min. After 2 h stirring at −78 °C, the reaction was quenched with sat. NH_4Cl (20 mL) and allowed to warm up to rt. The aqueous phase was washed three times with 30 mL of Et_2O, the combined organic phases were washed once with brine (20 mL) and dried with Na_2SO_4. The product was purified by flash column chromatography (30% EtOAc/hexane) affording **3** 3.25 g (63%). R_f (50% EtOAc/hexane, UV/PMA)=0.49; IR (ν_{max}, film) 1141, 1366, 1386, 1581, 1598, 1737, 3565 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.25 (t, J=7.1 Hz, 3H), 1.29 (s, 3H), 1.32 (s, 3H), 3.15 (d, J=6.6 Hz, 1H), 4.05 (m, 1H), 4.14 (dd, J=7.1, 4.9 Hz, 2H), 4.37 (dd, J=7.3, 11.7 Hz, 1H), 4.48 (dd, J=2.9, 11.7 Hz, 1H), 7.44 (m, 2H), 7.57 (m, 1H), 8.06 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 20.9, 22.6, 45.4, 61.0, 66.2, 75.1, 128.4, 128.9, 129.7, 133.1, 166.7, 176.8; HRMS (TOF MS EI$^+$) calcd for $C_{15}H_{21}O_5Na$ 303.1208, found 303.1221.

4.1.2. 4-(Benzyloxy)-dihydro-3,3-dimethylfuran-2(3*H*)-one 4. NaH (60% oil dispersion, 476 mg, 11.9 mmol, 110 mol%) in dry DMF was cooled to 0 °C. Ester **3** (3.03 g, 10.8 mmol, 100 mol%) in THF (6 mL) was added dropwise at 0 °C. The reaction mixture was stirred for 5 min at 0 °C and 15 min at rt. BnCl (1.37 mL, 11.9 mmol, 110 mol%) was added dropwise and the reaction was stirred for 4 h at rt. After quenching at 0 °C with sat. NH_4Cl, the aqueous phase was extracted three times with 25 mL of Et_2O, the combined organic phases were washed once with brine (50 mL) and dried with $MgSO_4$. After flash column chromatography (15% EtOAc/hexane) lactone **4** was isolated (1.77 g, 75%). R_f (30% EtOAc/hexane, UV/PMA)=0.27; IR (ν_{max}, film) 1773 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.26 (s, 3H), 1.28 (s, 3H), 3.91 (dd, J=4.0, 5.1 Hz, 1H), 4.15 (dd, J=4.0, 10.1 Hz, 1H), 4.31 (dd, J=5.1, 10.1 Hz, 1H), 4.59 (d, J_{AB}=

11.1 Hz, 2H), 7.30–7.39 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.9, 23.3, 42.9, 68.9, 72.1, 81.8, 127.5, 128.0, 128.5, 137.4, 180.6; HRMS (EI^+) calcd for $C_{13}H_{16}O_3$ 220.1099, found 220.1092.

4.1.3. 4-(Benzyloxy)-tetrahydro-3,3-dimethylfuran-2-ol 5. Lactone **4** (0.273 g, 1.24 mmol, 100 mol%) in toluene (12 mL) was cooled to −78 °C. DIBAL-H (1 M in toluene, 2.11 mL, 2.11 mmol, 170 mol%) was added during 5 min. After 14 min, the reaction was quenched by adding MeOH (0.5 mL) and allowed to warm up to rt. The solution was partitioned between 20 mL of 1 M HCl and 20 mL of EtOAc, the phases were separated and the aqueous phase was extracted three times with 15 mL of EtOAc. The combined organic phases were washed once with 10 mL of brine, dried with $MgSO_4$ and evaporated affording crude **5** 0.267 g, which was used without purification in the next reaction. R_f (50% EtOAc/hexane, UV/PMA)=0.36; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.01 (s, 3H), 1.24 (s, 3H), 3.58 (d, J=12.1 Hz, 1H), 3.61 (d, J=3.7 Hz, 1H), 4.05 (dd, J=10.5, 3.8 Hz, 1H), 4.23 (d, J=10.2 Hz, 1H), 4.54 (d, J_{AB}=11.8 Hz, 2H), 4.81 (d, J=11.9 Hz, 1H), 7.29–7.38 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.2, 24.0, 46.6, 70.9, 72.0, 85.3, 105.3, 127.6, 127.9, 128.5, 137.4; HRMS (TOF MS EI^+) calcd for $C_{13}H_{18}O_3Na$ 245.1154, found 245.1180.

4.1.4. 2-Benzyloxy-3,3-dimethylpent-4-yn-1-ol 7. Lactol **5** (0.214 g, 0.963 mmol, 100 mol%) was diluted in 10 mL of dry MeOH and dimethyl 1-diazo-2-oxopropyl phosphonate **6** (0.370 g, 1.925 mmol, 200 mol%) and K_2CO_3 (0.266 g, 1.925 mmol, 200 mol%) were added. The reaction was warmed to 36 °C and allowed to stir for 5 days, during which more phosphonate **6** (0.092 g, 0.481 mmol, 50 mol%) and K_2CO_3 (0.067 g, 0.481 mmol, 50 mol%) in 0.5 mL of dry MeOH were added five times once a day. The blue–green reaction mixture was evaporated to dryness and dissolved in 30 mL of 1:1 mixture of Et_2O and H_2O. The phases were separated and the aqueous one was extracted four times with 10 mL of Et_2O and dried with $MgSO_4$. Crude **7** was purified by column chromatography (15% EtOAc/hexane) affording 0.122 g (58%) of a slightly yellow oil. R_f (50% EtOAc/Hex, UV/anisaldehyde)=0.50; IR (ν_{max}, film) 1096, 1382, 2254, 3306, 3690 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.27 (s, 3H), 1.30 (s, 3H), 1.86 (dd, J=7.3, 5.3 Hz, 1H), 2.19 (s, 1H), 3.40 (dd, J=6.6, 3.8 Hz, 1H), 3.77 (ddd, J=11.9, 6.6, 5.3 Hz, 1H), 3.92 (ddd, J=11.7, 7.5, 3.9 Hz, 1H), 4.75 (d, J_{AB}=11.9 Hz, 2H), 7.29–7.38 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.7, 26.7, 34.7, 62.6, 69.8, 74.7, 85.6, 89.7, 127.8, 127.9, 128.5, 138.3; HRMS (TOF MS EI^+) calcd for $C_{14}H_{18}O_2NaSi$ 241.1204, found 241.1216.

4.1.5. (2-(Benzyloxy)-3,3-dimethylpent-4-ynyloxy)-*tert*-butyldimethylsilane 8. The alcohol **7** (0.120 g, 0.550 mmol, 100 mol%) was dissolved in dry CH_2Cl_2 (6 mL) and cooled to 0 °C. 2,6-Lutidine (0.256 mL, 2.2 mmol, 400 mol%) was added and the reaction mixture was allowed to stir for 36 min before TBSOTf (0.253 mL, 1.1 mmol, 200 mol%) was added. After 12 min the reaction was quenched with 3 mL of sat. K_2CO_3. The mixture was partitioned between water (10 mL) and Et_2O (10 mL) and the phases were separated. The aqueous phase was extracted three times with 10 mL of Et_2O and the combined organic phase dried with Na_2SO_4. Crude **8** was purified by column chromatography (15% EtOAc/hexane) affording pure product (0.161 g, 88%) as a slightly yellow oil. R_f (50% EtOAc/hexane, UV/PMA)=0.67; IR (ν_{max}, film) 839, 1096, 1257, 1383, 2254, 3306, 3690 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.07 (s, 3H), 0.08 (s, 3H), 0.92 (s, 9H), 1.20 (s, 3H), 1.27 (s, 3H), 2.13 (s, 1H), 3.36 (dd, J=7.3, 2.7 Hz, 1H), 3.80 (dd, J=10.8, 7.3 Hz, 1H), 4.10 (dd, J=10.8, 2.7 Hz, 1H), 4.78 (d, J_{AB}=11.4 Hz, 2H), 7.24–7.38 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.4, −5.3, 18.2, 24.4, 25.9, 27.1, 34.7, 65.4, 69.1, 74.5, 86.1, 90.0, 127.3, 127.8, 128.2, 139.0; HRMS (TOF MS EI^+) calcd for $C_{20}H_{32}O_2NaSi$ 355.2069, found 355.2110.

4.1.6. (*S*)-4-Benzyl-3-((2*S*,3*R*)-5-benzyloxy-3-hydroxy-2-methylpentanoyl)-2-oxazolidinone 10. (*S*)-4-Benzyl-3-propionyl-2-oxazolidinone **9** was dissolved in 100 mL of dry CH_2Cl_2 and cooled to 0 °C before dibutylboron triflate (1 M in CH_2Cl_2, 41.2 mL, 41.2 mmol, 120 mol%) was added dropwise keeping the internal temperature below 2 °C. The color changed to dark red-brown but when Et_3N (6.23 mL, 44.7 mmol, 130 mol%) was added (T ≤ 2 °C) it turned to yellow. After 40 min, the reaction mixture was cooled to −77 °C and 3-benzyloxy-propionaldehyde (6.2 g, 37.8 mmol, 110 mol%) dissolved in 10 mL CH_2Cl_2 was added slowly (45 min) keeping the internal temperature stable. Stirring was continued for a further 3 h at −77 °C and then for 30 min at 0 °C. Phosphate buffer (80 mL, pH 7.0) and methanol (60 mL) were added, and the mixture was cooled to −10 °C before slow (15 min) addition of 120 mL of (1:1) H_2O_2 (30%) and MeOH. The mixture was then stirred for 30 min at 0 °C before organic solvents were evaporated, Et_2O was added and reaction was cooled to 0 °C. Sat. $Na_2S_2O_3$ (120 mL) was added slowly (30 min) and the phases were separated. The aqueous phase was extracted three times with 80 mL Et_2O and the combined organic phases were washed once with 80 mL of sat. $NaHCO_3$ and 50 mL of brine and dried with Na_2SO_4. The crude product was purified by flash column chromatography (25% EtOAc/Hex) affording pure **10** (9.7 g, 71%). R_f (50% EtOAc/Hex, UV/PMA)=0.31; $[\alpha]_D^{20}$=+44.7 (*c* 1.0; $CHCl_3$); IR (ν_{max}, film) 1111, 1694, 1780, 3480 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.28 (d, J=7.0 Hz, 3H), 1.74 (m, 1H), 1.89 (m, 1H), 2.78 (dd, J=13.2, 9.5 Hz, 1H), 3.26 (dd, J=13.5, 3.3 Hz, 1H), 3.29 (d, J=2.6 Hz, 1H), 3.69 (m, 2H), 3.82 (dq, J=7.0, 3.7 Hz, 1H), 4.18 (m, 1H), 4.19 (m, 2H), 4.52 (s, 2H), 4.68 (m, 1H), 7.34–7.19 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.1, 33.7, 37.8, 42.6, 55.2, 66.1, 68.4, 70.4, 73.3, 127.4, 127.7, 128.4, 129.0, 129.4, 135.1, 138.0, 153.1, 176.7; HRMS (EI^+) calcd for $C_{23}H_{27}NO_5$ 397.1889, found 397.1880.

4.1.7. (2*S*,3*R*)-5-(Benzyloxy)-3-hydroxy-*N*-methoxy-*N*,2-dimethylpentanamide 11. A 25 mL 2-neck flask was charged with *N*,*O*-Dimethyl hydroxylamine hydrochloride (1.08 g, 11.1 mmol, 220 mol%) and 4 mL THF. The suspension was cooled to −10 °C in a NaCl/ice-bath and $AlMe_3$ (5.3 mL, 10.6 mmol, 210 mol%) was added over 5 min. After 12 min, the cooling bath was removed and the reaction mixture was allowed to stir for 1 h at rt before it was cooled again to −10 °C. Oxazolidinone **10** (2.0 g, 5.0 mmol, 100 mol%) dissolved in a mixture (4:5) of CH_2Cl_2 (2.9 mL) and THF (3.5 mL) was slowly added.

The mixture was stirred for 1 h at 0 °C and then poured into a pre-cooled 0 °C mixture of aqueous HCl [0.5 M] (16 mL) and CH_2Cl_2 (16 mL). This was stirred for 1 h 15 min at 0 °C and the phases were separated. The aqueous phase was extracted three times with 60 mL of CH_2Cl_2 and the combined organic phases were washed once with 50 mL of brine and dried with $MgSO_4$. The crude product was purified by step gradient column chromatography (1:3, 2:5, 1:1 and 3:5 EtOAc / hexane in 900 mL fractions) affording **11** as a light yellow oil (1.16 g, 82%). R_f (50% EtOAc/Hex, UV/PMA)=0.12; $[\alpha]_D^{20}=+11.4$ (*c* 1.0; $CHCl_3$); IR (ν_{max}, film) 1102, 1637, 3468 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.20 (d, $J=7.3$ Hz, 3H), 1.89–1.66 (m, 2H), 2.93 (br s, 1H), 3.18 (s, 3H), 3.63–3.73 (m, 2H), 3.66 (s, 3H), 3.92 (s, 1H), 4.05 (m, 1H), 4.52 (s, 2H), 7.26–7.34 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.1, 31.9, 34.0, 39.5, 61.5, 68.3, 70.3, 73.2, 127.6, 127.6, 128.4, 138.2, 177.8; HRMS (TOF MS EI^+) calcd for $C_{15}H_{23}NO_4Na$ 304.1525, found 304.1550.

4.1.8. (2*S*,3*R*)-5-(Benzyloxy)-3-(*tert*-butyldimethylsilyloxy)-*N*-methoxy-*N*,2-dimethylpentanamide 12. Alcohol **11** (0.50 g, 1.78 mmol, 100 mol%) and imidazole (0.61 g, 8.89 mmol, 500 mol%) were dissolved in 5 mL of dry DMF and cooled to 0 °C. TBSCl (0.54 g, 3.55 mmol, 200 mol%) in 5 mL DMF was added dropwise over 10 min to the reaction after which the reaction was allowed warm up to rt. After stirring for 43 h, the reaction was quenched with 20 mL of EtOAc and 20 mL of brine and stirred for 30 min. The phases were separated and the aqueous phase was washed three times with 20 mL of Et_2O. The combined organic phases were dried over $MgSO_4$. The crude product was purified by column chromatography (5% MTBE/Hex) affording the product **12** (0.48 g, 68%). R_f (50% EtOAc/Hex, UV/PMA)=0.46; $[\alpha]_D^{20}=-2.4$ (c 1.0; $CHCl_3$); IR (ν_{max}, film) 836, 1103, 1663 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.04 (s, 3H), 0.06 (s, 3H), 0.89 (s, 9H), 1.13 (d, $J=$ 7.0 Hz, 3H), 1.82–1.88 (m, 2H), 2.99 (br s, 1H), 3.13 (s, 3H), 3.49–3.56 (m, 2H), 3.59 (s, 3H), 4.03 (td, $J=8.0$, 5.1 Hz, 1H), 4.47 (d, $J_{AB}=12.1$ Hz, 2H), 7.24–7.33 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.5, −4.4, 14.5, 18.1, 25.9, 32.1, 35.4, 41.2, 61.2, 66.5, 71.3, 72.9, 127.4, 127.7, 128.3, 138.6, 176.3; HRMS (EI^+) calcd for $C_{21}H_{37}NO_4Si$ 395.2492, found 395.2512.

4.1.9. (3*R*,4*S*,9*R*/*S*)-1,9-Bis(benzyloxy)-3,10-di(*tert*-butylsilyloxy)-4,8,8-trimethyldec-6-yn-5-one 13a,b. The alkyne **8** (0.057 g, 0.172 mmol, 200 mol%) was dissolved in 1.7 mL of dry THF and cooled to −78 °C. BuLi (2.27 M, 83 µl, 0.189 mmol, 220 mol%) was added and the reaction was allowed to stir for 1 h before the Weinreb amide **12** (0.034 g, 0.086 mmol, 100 mol%) in 0.9 mL of dry THF was added. After 50 min, the reaction mixture was allowed to warm up to rt and after another 2 h 15 min it was quenched with 5 mL of H_2O. Et_2O (10 mL), H_2O (5 mL) and brine (5 mL) were added and the phases were separated. The aqueous phase was extracted three times with 10 mL of Et_2O and the combined organic phases were dried with $MgSO_4$. The crude product was purified by step gradient chromatography (150 mL 5% EtOAc/hexane, 150 mL 10% EtOAc/hexane) affording **13a,b** (0.045 g, 79%). R_f (50% EtOAc/Hex, UV/PMA)=0.66; IR (ν_{max}, film) 838, 1095, 1257, 1669, 2208, 2247 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.01 (s, 3H), 0.04 (s, 3H), 0.06 (s, 3H), 0.07 (s, 3H), 0.84 (s, 9H), 0.91 (s, 9H), 1.13 (d, $J=6.9$ Hz, 3H), 1.23 (s, 3H), 1.28 (s, 3H), 1.76–1.92 (m, $J=14.0$, 6.4 Hz, 2H), 2.53–2.60 (m, $J=13.9$, 6.9 Hz, 1H), 3.38 (dd, $J=7.1$, 3.0 Hz, 1H), 3.49 (t, $J=6.5$ Hz, 2H), 3.78 (dd, $J=10.8$, 7.1 Hz, 1H), 4.00 (dd, $J=10.8$, 3.0 Hz, 1H), 4.75 (d, $J_{AB}=11.5$ Hz, 2H), 7.25–7.35 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.4, −5.4, −4.5, −4.4, 9.5, 9.6, 18.1, 18.2, 23.9, 24.0, 25.8, 25.9, 26.1, 35.4, 35.7, 53.5, 65.1, 65.1, 66.7, 70.0, 73.0, 74.5, 81.3, 85.5, 85.5, 99.3, 127.4, 127.4, 127.5, 127.7, 127.7, 128.2, 128.3, 138.4, 138.7, 138.8, 190.2; HRMS (TOF MS EI^+) calcd for $C_{39}H_{62}O_5NaSi_2$ 689.4034, found 689.4025.

4.1.10. (7*R*,8*S*)-3-Benzyloxy-7-(2-benzyloxy-ethyl)-4,4,8-trimethyl-1,6-dioxa-spiro[4.5]decan-9-one 1a and 1b. The mixture of ynones **13a,b** (13 mg, 19.5 µmol, 100 mol%) was dissolved in 0.5 mL of dry MeOH, and camphor sulphonic acid (0.7 mg, 3.0 µmol, 15 mol%) was added. The reaction was allowed to stir at rt for 2 h 20 min before the solvent was evaporated. The residue was dissolved in 1 mL benzene and the reaction was stirred for 3 h 30 min, after which time *p*-TsOH (1.4 mg, 7.4 µmol, 38 mol%) was added. Stirring was continued for another 15 h, and the reaction was quenched by adding TEA (0.02 mL) followed by 1 mL of sat. $NaHCO_3$. The phases were separated and the aqueous one was extracted three times with 3 mL of toluene. The combined organic phases were extracted once with 5 mL of brine and dried with $MgSO_4$. The crude product was first purified by step gradient column chromatography (5, 10, 15 and 20% EtOAc/hexane in 50 mL portions) affording the two diastereomers **1a** and **1b** (8.2 mg, 96%). The diastereomers were separated with HPLC chromatography, which afforded (4.1 mg each).

(Fraction 1) R_f (50% EtOAc/Hex, UV/PMA)=0.59; R_t (Shandon Hypersil 5µ column, EtOAc/hexane, 1:20, flow rate 1.0 mL/min, $\lambda=254$ nm)=30.52 min; $[\alpha]_D^{20}=+105$ (*c* 0.1; $CHCl_3$); IR (ν_{max}, film) 1718 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.94 (s, 3H), 1.07 (d, $J=7.0$ Hz, 3H), 1.60 (s, 3H), 1.64–1.72 (m, 1H), 1.81–1.90 (m, 1H), 2.33 (qd, $J=7.0$, 2.6 Hz, 1H), 2.45 (dd, $J_{AB}=14.8$ Hz, 2H), 3.46–3.54 (m, 2H), 3.59 (dd, $J=8.8$, 6.7 Hz, 1H), 3.59 (dd, $J=8.7$, 7.8 Hz, 1H), 4.12 (dd, $J=7.7$, 6.7 Hz, 1H), 4.24 (td, $J=9.8$, 3.0 Hz, 1H), 4.47 (dd, $J_{AB}=11.9$ Hz, 2H), 4.49 (dd, $J_{AB}=11.8$ Hz, 2H), 7.28–7.35 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.5, 17.2, 20.3, 29.7, 40.8, 47.6, 66.9, 67.2, 69.3, 72.9, 73.1, 84.5, 110.0, 127.4, 127.7, 127.7, 128.4, 128.4, 138.2, 138.4, 209.9; HRMS (TOF MS EI^+) calcd for $C_{27}H_{34}O_5Na$ 461.2304, found 461.2318.

(Fraction 2) R_f (50% EtOAc/Hex, UV/PMA)=0.59; R_t (Shandon Hypersil 5µ column, EtOAc/hexane, 1:20, flow rate 1.0 mL/min, $\lambda=254$ nm)=35.69 min; $[\alpha]_D^{20}=+90$ (*c* 0.1; $CHCl_3$); IR (ν_{max}, film) 1718 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.91 (s, 3H), 1.11 (d, $J=7.1$ Hz, 3H), 1.25 (s, 3H), 1.59–1.67 (m, 1H), 1.85–1.94 (m, 1H), 2.34 (qd, $J=7.2$, 2.0 Hz, 1H), 2.42 (dd, $J_{AB}=14.5$ Hz, 2H), 3.54–3.67 (m, 2H), 3.61 (dd, $J=6.4$, 3.1 Hz, 1H), 3.67 (dd, $J=9.7$, 3.2 Hz, 1H), 4.16 (dd, $J=9.7$, 6.4 Hz, 1H), 4.28 (td, $J=10.6$, 2.5 Hz, 1H), 4.30 (dd, $J_{AB}=12.1$ Hz, 2H), 4.49 (dd, $J_{AB}=12.1$ Hz, 2H), 7.23–7.36 (m, 10H); ^{13}C NMR

(100 MHz, $CDCl_3$) δ 10.7, 16.6, 24.5, 29.7, 41.1, 49.0, 66.6, 67.0, 71.3, 72.5, 72.8, 85.4, 108.8, 127.1, 127.4, 127.5, 127.5, 128.3, 128.3, 128.4, 138.6, 138.6, 210.4; HRMS (TOF MS EI^+) calcd for $C_{27}H_{34}O_5Na$ 461.2304, found 461.2317.

Acknowledgements

Funding and financial support provided by the Finnish Academy, the Ministry of Education, Jenny and Antti Wihuri Foundation and Emil Aaltonen Foundation are gratefully acknowledged. We would like to thank Mr. Y. Masuda for the valuable work with the lactone fragment and Päivi Joensuu at the University of Oulu for providing the high resolution mass spectroscopy data.

References and notes

1. For reviews of spiroketals see: (a) Perron, F.; Albizati, K. F. *Chem. Rev.* **1989**, *89*, 1617–1661. (b) Jacobs, M. F.; Kitching, W. *Curr. Org. Chem.* **1998**, *2*, 395–436.
2. This is not always the case; e.g. (a) Pectenotoxin-1: Yasumoto, T.; Murata, M.; Oshima, Y.; Sano, M.; Matsumoto, G. K.; Clardy, J. *Tetrahedron* **1985**, *41*, 1019. (b) Erythronolide A anhydride: Schomburg, D.; Hopkins, P. B.; Lipscomb, W. N.; Corey, E. J. *J. Org. Chem.* **1980**, *45*, 1544. (c) Endusamycin: Oscarson, J. R.; Bordner, J.; Celmer, W. D.; Cullen, W. P.; Huang, L. H.; Maeda, H.; Moshier, P. M.; Nishiyama, S.; Presseau, L.; Shibakawa, R.; Tone, J. *J. Antibiot.* **1989**, *42*, 37.
3. (a) Koskinen, A. M. P.; Pihko, P. M. *Curr. Trends Org. Synth.* **1999**, 291–298. (b) Pihko, P. M.; Koskinen, A. M. P. *Synlett* **1999**, 1966–1968. (c) Pihko, P. M.; Koskinen, A. M. P.; Nissinen, M. J.; Rissanen, K. *J. Org. Chem.* **1999**, *64*, 652–654. (d) Pihko, P. M.; Koskinen, A. M. P. *J. Org. Chem.* **1998**, *63*, 92–98. (e) Koskinen, A. M. P.; Pihko, P. M. *Tetrahedron Lett.* **1994**, *35*, 7417–7420. (f) Koskinen, A. M. P.; Chen, J. *Tetrahedron Lett.* **1991**, *32*, 6977–6980. (g) Lindvall, M. K.; Pihko, P. M.; Koskinen, A. M. P. *J. Biol. Chem.* **1997**, *272*, 23312–23316. (h) Karisalmi, K.; Koskinen, A. M. P.; Nissinen, M.; Rissanen, K. *Tetrahedron* **2003**, *59*, 1421–1427.
4. Kato, Y.; Fusetani, N.; Matsunaga, V.; Hashimoto, V.; Fujita, V.; Furuya, V. *J. Am. Chem. Soc.* **1986**, *108*, 2780–2781.
5. For previous synthetic approaches, see: (a) Anderson, O. P.; Barrett, A. G. M.; Edmunds, J. J.; Hachiya, S.-I.; Hendrix, J. A.; Horita, K.; Malecha, J. W.; Parkinson, C. J.; VanSickle, A. *Can. J. Chem.* **2001**, *79*, 1562–1592. (b) Evans, D. A.; Gage, J. R. *Tetrahedron Lett.* **1990**, *31*, 6129–6132. (c) Evans, D. A.; Gage, J. R.; Leighton, J. L. *J. Am. Chem. Soc.* **1992**, *114*, 9434–9453. (d) Barrett, A. G. M.; Edmunds, J. J.; Horita, K.; Parkinson, C. J. *J. Chem. Soc., Chem. Commun.* **1992**, 1236–1238. (e) Tanimoto, N.; Gerritz, S. W.; Sawabe, A.; Noda, T.; Filla, S. A.; Masamune, S. *Angew. Chem.* **1994**, *106*, 674–677. See also *Angew. Chem., Int. Ed. Engl.*, **1994**, *33*, 673–675. (f) Yokokawa, F.; Hamada, Y.; Shioiri, T. *Chem. Commun.* **1996**, 871–872. (g) Smith, A. B.; Friestad, G. K.; Barbosa, J.; Bertounesque, E.; Hull, K. G.; Iwashima, M.; Qiu, Y.; Salvatore, B. A.; Spoors, P. G.; Duan, J. J.-W. *J. Am. Chem. Soc.* **1999**, *121*, 10468–10477. (h) Smith, A. B.; Iwashima, M. *Tetrahedron Lett.* **1994**, *35*, 6051–6052. (i) Smith, A. B.; Duan, J. J. W.; Hull, K. G.; Salvatore, B. A. *Tetrahedron Lett.* **1991**, *32*, 4855–4858. (j) Scarlato, G. R.; DeMattei, J. A.; Chong, L. S.; Ogawa, A. K.; Lin, M. R.; Armstrong, R. W. *J. Org. Chem.* **1996**, *61*, 6139–6152. (k) Trost, B. M.; Flygare, J. A. *Tetrahedron Lett.* **1994**, *35*, 4059–4062.
6. (a) Aiguade, J.; Hao, J.; Forsyth, C. J. *Org. Lett.* **2001**, *3*, 979–982. (b) Forsyth, C. J.; Hao, J.; Aiguade, J. *Angew. Chem., Int. Ed.* **2001**, *40*, 3663–3667. (c) Forsyth, C. J. *Tetrahedron Lett.* **2002**, *43*, 1–2.
7. (a) Seyferth, D.; Marmor, R. S.; Hilbert, P. *J. Org. Chem.* **1971**, *36*, 1379. (b) Gilbert, J. C.; Weerisooriya, U. *J. Org. Chem.* **1982**, *47*, 1837.
8. (a) Ohira, S. *Synth. Commun.* **1989**, *19*, 561–564. (b) Kitamura, M.; Tokunaga, M.; Noyori, R. *J. Am. Chem. Soc.* **1995**, *117*, 2931–2932.Regitz, M.; Hocker, J.; Liedhegener, A. *Organic Synthesis*, *Collect. Vol. V*, pp 179–183 (d) Meffre, P.; Hermann, S.; Durand, P.; Reginato, G.; Riu, A. *Tetrahedron* **2002**, *58*, 5159–5162. (e) Kerr, W. J.; McLaughlin, M.; Morrison, A. J.; Pauson, P. L. *Org. Lett.* **2001**, *3*, 2945–2948. (f) Müller, S.; Liepold, B.; Roth, G. J.; Bestmann, H. J. *Synlett* **1996**, 521–522.
9. See use of lactols as aldehyde surrogates, see e.g. (a) Schmidlin, J.; Wettstein, A. *Helv. Chim. Acta* **1963**, *46*, 2799–2810. (b) Corey, E. J.; Weinshenker, N. M.; Schaaf, T. K.; Huber, W. *J. Am. Chem. Soc.* **1969**, *97*, 5675–5677.
10. Corey, E. J.; Venkateswarlu, A. J. *J. Am. Chem. Soc.* **1972**, *94*, 6190.
11. Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815–3818.