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A versatile route to conjugated hydroxy (*E,Z,E,E*)-tetraenoic acids: highly chemo- and stereoselective synthesis of lipoxin B_4

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Abstract: A highly convergent total stereocontrolled synthesis of lipoxin B_4 is described by an efficient Pd-catalyzed coupling reaction of two easily accessible chiral synthons **2** and **3** without any protection–deprotection sequence of the alcohol functions. © 1997 Elsevier Science Ltd

Due to the importance of conjugated polyenes in the field of biologically active compounds,[1] the development of new approaches for the synthesis of such highly unsaturated derivatives is of great interest. One of today's challenges in this field is to devise and develop chemoselective reactions which can produce diversely stereodefined functionalized polyene compounds with excellent stereoselectivity. We have recently reported that sequential coupling of 1,2-dichloroethylene with 1-alkynes under Pd-catalysis followed by stereoselective reduction of the triple bonds is a versatile procedure for the preparation of a variety of conjugated polyenes.[2]

The lipoxins, which are a series of biologically active compounds formed from arachidonic acid in human polymorphonuclear leukocytes,[3] are characterized by the presence of a conjugated tetraenic triol system. Due to their extreme scarcity from biosynthetic routes, there is a need to develop a general strategy which should lead stereoselectively to the desired isomer. The Wittig reaction has often been utilized[4] however, it is not totally chemo- and stereoselective and isolation of pure isomers by chromatography is usually required. We wish to report herein our approach towards the naturally occurring lipoxin LXB_4 **1a** (namely the (5*S*, 14*R*, 15*S*)-trihydroxy-(6*E*, 8*Z*, 10*E*, 12*E*)-eicosatetraenoic acid). Preliminary results have been reported;[5] the characteristic feature of our synthesis, summarized in Scheme 1, is based:

(1) on the highly enantioselective and practical preparation of the unprotected chiral synthons **2** and **3**;

(2) on the stereospecific construction of the conjugated tetraene framework by palladium–copper catalysis without any protection–deprotection sequence of the alcohol functions.

Results and discussion

The tetraene framework could be obtained according to two different synthetic approaches (path a or b, Scheme 1). In order to evaluate the best route to the conjugated tetraene unit, we planned to synthesize the analog **11** containing the racemic diol functions as outlined in Scheme 2.

Our synthesis of the required analog **11a** starts with the hydroxyenyne **9a**, conveniently obtained from known chlorodiene **8**[6] by treatment with *n*-BuLi (3 equiv) in THF.[7] Thus, the coupling of **8** with **9a** in piperidine in the presence of bis(benzonitrile)palladium chloride[8] and copper iodide gave the trienyne **10a** (50%) which was stereoselectively reduced into the pure tetraene **11a** (54%) by activated zinc.[9] Attempts to prepare the tetraene **11b** bearing an ester group under the same strategy were

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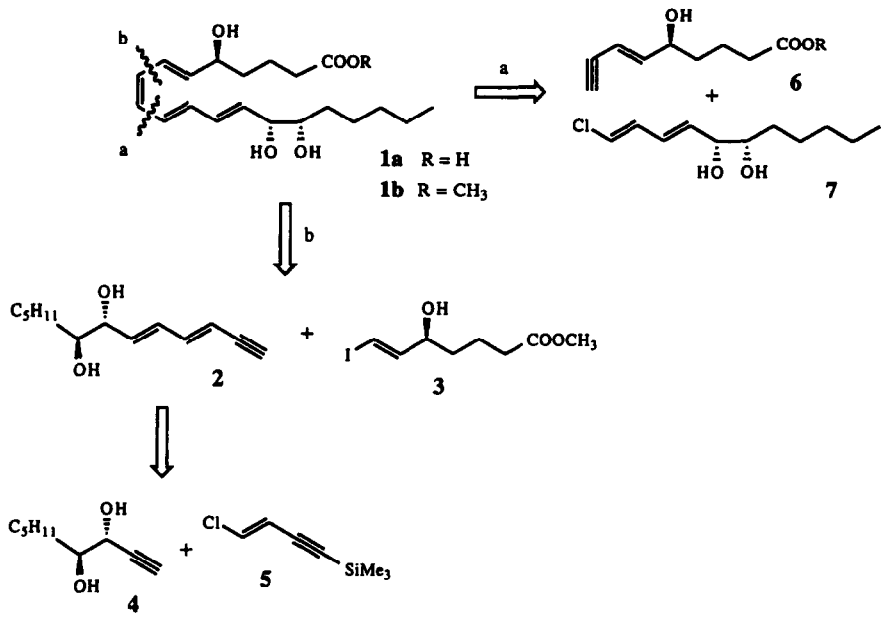
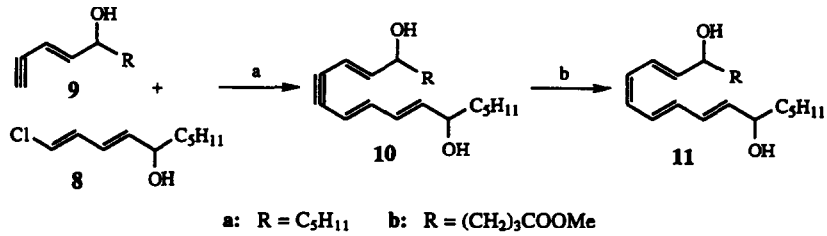
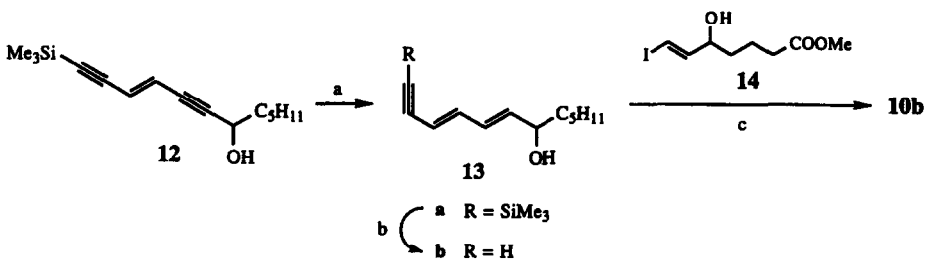


Scheme 1.



Scheme 2. (a) $PdCl_2(PhCN)_2$ 5%, CuI 10%, piperidine, 20°C; (b) Zn (Cu/Ag), MeOH/H_2O 1/1, 30°C, 15 h.

unsuccessful. Difficulties in coupling the derivative **9b** with **8** led us to explore a second synthetic approach starting from the iodo vinyl alcohol **14**[10] and the hydroxy dienyne **13b** as outlined in Scheme 3.



Scheme 3. (a) Red-Al (1.6 equiv), ether, 0° to 20°C, 2 h, 80%; (b) $AgNO_3$, KCN, EtOH, H_2O, THF, 86%; (c) **14** (1 equiv) $Pd(PPh_3)_4$ 5%, CuI 10%, piperidine (2 equiv), C_6H_6, 60%.

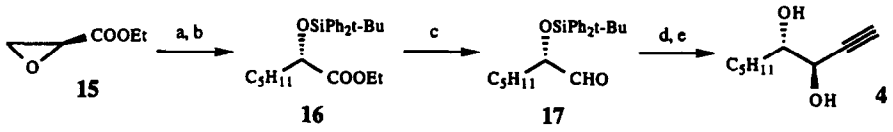
The synthesis of **13a** was achieved stereoselectively by Pd–Cu catalyzed sequential coupling of (*E*)-1,2-dichloroethylene with 1-butyn-3-ol and trimethylsilyl acetylene[11] followed by stereoselective reduction of the propargylic alcohol function. After desilylation,[12] the coupling of **13b** with the vinyl

iodide[10] **14** in the presence of tetrakis(triphenylphosphine) palladium led in good yield to the desired compound **10b** (Scheme 3).

Total synthesis of lipoxin B_4

In order to prepare the diol **2** in a convergent manner, we planned to couple the *anti*-acetylenic diol **4** with the chloroenyne **5** which is readily obtained in 82% yield from (*E*)-dichloroethylene and trimethylsilylacetylene in the presence of tetrakis(triphenylphosphine) palladium and cuprous iodide[11d,e] (Scheme 1).

The required *anti*-acetylenic diol **4** (Scheme 4) was obtained by condensation of a metallated trimethylsilyl monoprotected acetylene with the enantiomerically pure O-protected α-hydroxyaldehyde **17** easily prepared by DIBAL-H reduction at low temperature of the corresponding O-silyl α-hydroxyester **16** obtained from the reaction of ethyl glycidate **15** with magnesium homocuprate.[13] Such a reaction generally affords a mixture of *syn*- and *anti*-diastereomers. However, the reaction of zinc acetylides with O-benzyloxyaldehydes has been reported to give mainly the *syn*-isomers,[14] a result in agreement with the formation of a chelated intermediate. We thought that, using a non-chelating protective group such as a silyl ether, it would be possible to inverse this diastereoselectivity and to obtain the *anti*-isomer in accordance with the Felkin–Anh model.[15]



Scheme 4. (a) $Bu_2CuMgBr$, THF, 1 h, −70°C, 86%; (b) *t*-$BuPh_2SiCl$, imidazole, DMF, 90%; (c) DIBAL-H, pentane, 4 h, −70°C, 91%; (d) $Me_3SiC{\equiv}CLi$, THF–HMPA, 80% (anti+syn); (e) TBAF, THF 65% after recrystallisation.

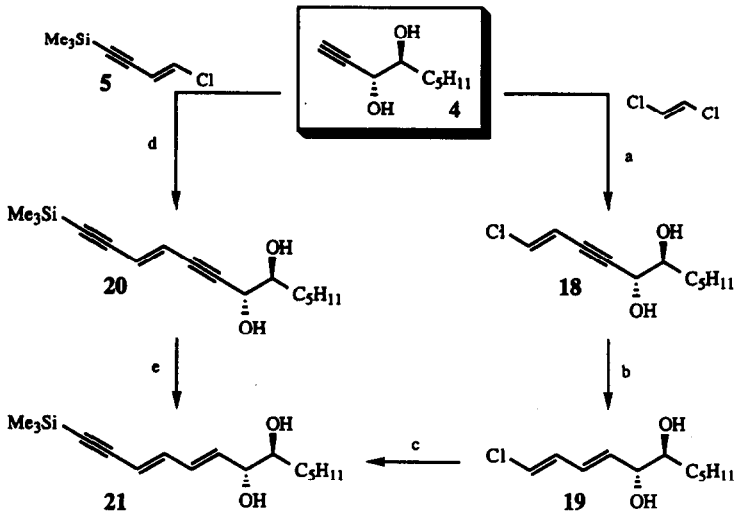
Whereas the condensation of lithium silyl acetylide with the O-benzyl 2-hydroxyhexanal gives the resulting diols in a *syn/anti* 50/50 ratio, the use of *t*-butyldiphenylsilyl protective group allows the formation of the *anti*-isomer mainly (*syn/anti*: 27/73). Moreover, this ratio could be improved by addition of a dissociating agent such as HMPA (16/84; 80% yield) or 12-crown-4 (16/84; 54% yield). Unexpectedly, the use of sodium acetylide (even in the presence of HMPT or crown-ether) did not allow this *anti/syn* ratio to be increased.

In contrast with results previously reported,[16] we did not succeed in reacting titanated acetylides with the O-silylated α-alkoxyaldehydes.

In order to determine the stereochemistry of this condensation, it was necessary to desilylate the resulting monoprotected diols. Indeed, during the reaction of the aldehyde with the acetylide we observed a mixture of silylated compounds resulting from a partial transfer of the silyl group from the protected alcohol to the lithium alcoholate. This desilylation was achieved with tetrabutylammonium fluoride in THF and gave exclusively the acetylenic diols in crystalline form. After one recrystallisation, the pure *anti*-isomer was isolated in an enantiomeric purity better than 99%.[17]

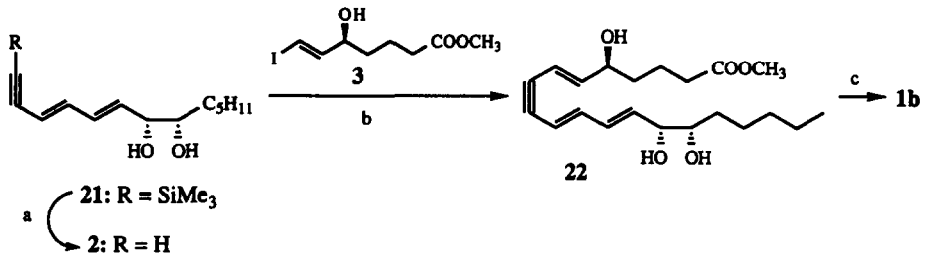
The enantiomerically pure compound **21** was synthesized as outlined in Scheme 5. The coupling reaction of (*E*)-1,2-dichloroethylene with the *anti*-diol **4** under palladium catalysis[11] afforded in 76% yield the diol **18** which was conveniently reduced selectively into the corresponding chlorodienol **19** with lithium aluminium hydride.[18] The coupling of this unprotected diol **19** with trimethylsilyl acetylene using $PdCl_2(PhCN)_2$ and CuI as catalysts in piperidine afforded the diol **21** in low yield (37%, Scheme 5) moreover, the results obtained for this reaction were rather erratic; in some cases we observed the formation of the (*E,Z*)-isomer along with the required (*E,E*)-isomer. This non-stereoselective approach prompted us to look for a more convergent and convenient strategy to prepare stereoselectively the key intermediate **21**. Thus, the coupling of **4** with chloroenyne **5**[11e] under Pd–Cu catalysis[8] in piperidine–THF produced exclusively the *trans*-enediyne **20** (75% yield). Stereoselective

reduction of the propargylic alcohol function gave the pure (*E,E*)-diene **21**. It was found necessary to carry out this reaction with Red-Al[19] instead of $LiAlH_4$ in order to obtain complete reduction.



Scheme 5. (a) $Pd(PPh_3)_4$ 5%, CuI 10%, (*E*)-ClCH=CHCl 3 equiv, piperidine 2 equiv, C_6H_6, 20°C, 76%; (b) $LiAlH_4$, THF, 65°C, 3h, 63%; (c) $PdCl_2(PhCN)_2$ 5%, CuI 10%; $Me_3SiC{\equiv}CH$ 2 equiv, piperidine, 20°C, 37%; (d) $PdCl_2(PhCN)_2$ 7%, CuI 10%, piperidine 20 equiv, THF, 20°C, 75%; (e) Red-Al, Et_2O, 20°C, 74%.

Finally, the pure (*E,E*) desired unprotected diol **2** was obtained in a quantitative yield by treatment of trimethylsilylated acetylenic compound **21** with KCN and $AgNO_3$[12] at 0°C. Chemoselective coupling of **2** with the known optically active vinyl iodide **3** previously synthesized,[10] in the presence of $Pd(PPh_3)_4$ and CuI afforded sterespecifically the conjugated trienyne **22** (55% yield)[20] which was stereoselectively reduced by activated zinc[9] into the pure (*E,Z,E,E*)-tetraene **1b** in 72% yield (Scheme 6).



Scheme 6. (a) $AgNO_3$-KCN, EtOH, H_2O, THF, 98%; (b) $Pd(PPh_3)_4$ 5%, CuI 10%, piperidine 2 equiv, C_6H_6, 20°C, 55%; (c) Zn (Cu/Ag), MeOH/H_2O 1/1, 30°C, 15 h, 72%.

In conclusion, this highly convergent synthesis led to the lipoxin B_4 in appreciable amounts, in a limited number of steps. Furthermore, it appears to be a stereoselective route to polyenic alcohols without involving any protection–deprotection sequence of the alcohol functions.

Experimental

Products were purified by distillation or by medium pressure liquid chromatography on a Jobin–Yvon Modulprep (Kieselgel 60H Merck) or by flash chromatography (Kieselgel 60 Merck: 230–400 Mesh) and analyzed by GC (BP5, SGE, 25 m capillary column) or by TLC (silica gel 60F 254). Optical rotations were measured on a Perkin-Elmer 141 polarimeter. NMR spectra were

recorded on a Bruker AC 200 MHz, VM 250 or AM 400 instrument. $CDCl_3$ was used as solvent with TMS as internal standard. Mass spectra were recorded on a Nermag R 10-10 (fitted with a GC-mass coupling; column: CP Sil 5, Chrompack, 40 m). IR spectra were recorded on a Perkin-Elmer 599 spectrophotometer (neat, cm^{-1}).

(3E)-3-Decen-1-yn-5-ol ***9a***

A solution of chlorodiene[6] **8a** (16.0 mmol, 3.02 g) in 40 mL of THF was treated dropwise, at −10°C, with *n*-BuLi (48.0 mmol). After complete addition, the reaction was stirred at −10°C for 2 h. Then, the reaction was hydrolysed with H_2O (10 mL) and extracted with diethyl ether (2×20 mL). The organic extract was dried over $MgSO_4$ and the solvent was removed *in vacuo*. Filtration through silica gel (cyclohexane/AcOEt 95:5) gave 2.26 g (93%) of pure **9a**. IR (neat) cm^{-1} 3300, 1630, 2100; ^1H NMR (250 MHz, $CDCl_3$) δ 6.23 (dd, 1H, J=16.0 and 5.9 Hz), 5.67 (dt, 1H, J=16.0 and 2.0 Hz), 4.14 (qd, 1H, J=5.8 and 1.9 Hz), 2.87 (d, 1H, J=2.0 Hz), 1.81 (s, 1H), 1.50 (m, 2H), 1.43 to 1.20 (m, 6H), 0.87 (t, 3H, J=6.6 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 147.70, 108.40, 81.70, 77.70, 71.85, 36.70, 31.60, 24.80, 22.45, 13.90; CIMS (NH_3) m/e: 154, 152 ($(M)^+$, 100%), 135; Anal. calcd. for $C_{10}H_{16}O$: C, 78.90 H, 10.58 Found: C, 78.71, H, 10.65.

(7E,11E,13E)-7,11,13-Eicosatrien-9-yn-6,15-diol ***10a***

To a suspension of $PdCl_2(PhCN)_2$ (0.96 mmol, 367 mg), chlorodiene **8** (3 mmol, 566 mg) CuI (1.9 mmol, 365 mg) in piperidine (15 mL) was added via syringe pump (addition time 1.5 h) hydroxy enyne **9a** (6 mmol, 912 mg). After complete addition, the reaction was stirred at room temperature for 2 h and treated with a saturated solution of NH_4Cl (30 mL). The aqueous layer was extracted with ether (3×20 mL). The combined organic layers were washed successively with aqueous HCl (0.2 M, 15 mL), $NaHCO_3$ (10 mL) and H_2O (2×30 mL), dried over $MgSO_4$ and concentrated under vacuum. Purification by flash chromatography (cyclohexane/AcOEt 6:4) afforded the trienyne **10a** in 50% yield (283 mg). IR (neat) cm^{-1} 3450, 2985, 2860, 2170, 1620, 1110; ^1H NMR (250 MHz, $CDCl_3$) δ 6.51 (dd, 1H, J=15.4 and 10.8 Hz), 6.20 (dd, 1H, J=15.6 and 10.9 Hz), 6.08 (dd, 1H, J=15.9 and 6.1 Hz), 5.77 (m, 1H), 5.73 (dd, 1H, J=15.2 and 6.7 Hz), 5.65 (dd, 1H, J=15.8 and 1.2 Hz), 4.10 (q, 2H, J=6.0 Hz), 1.63 (s, 2H), 1.53 to 1.38 (m, 4H), 1.34 to 1.18 (m, 12H), 0.80 (t, 6H, J=6.5 Hz); ^{13}C NMR (50 MHz, $CDCl_3$): δ 145.65, 140.90, 138.95, 129.40, 111.35, 109.85, 90.50, 89.45, 72.30, 72.25, 37.15, 36.95, 31.75 (2C), 25.05, 25.00, 22.60 (2C), 14.05 (2C); CIMS (NH_3) m/e: 287 $(M+H^+-H_2O)^+$, 100%; Anal. calcd. for $C_{20}H_{32}O_2$: C, 78.90 H, 10.58 Found: C, 78.41, H, 9.98.

(7E,9Z,11E,13E)-7,9,11,13-Eicosatetraene-6,15-diol ***11a***

Activated zinc dust was prepared as previously described.[9] A solution of **10a** (0.427 mmol, 130 mg) in H_2O–MeOH 1:1 (6 mL) was added to the suspension of activated zinc (1 g) and stirred at 35°C for 12 h. The reaction mixture was filtered on a pad of Celite and concentrated. Ether (10 mL) was added and the organic layer washed with H_2O (2×5 mL), dried over $MgSO_4$ and the solvent was removed *in vacuo*. Purification by flash chromatography (cyclohexane/AcOEt 6:4) gave the pure tetraene **11a** in 54% yield (70 mg). IR (neat) cm^{-1} 3350, 3010, 1565, 1460, 960; ^1H NMR (250 MHz, $CDCl_3$) δ 6.70 and 6.56 (m, 2H), 6.32 and 6.08 (m, 2H), 6.02 and 5.88 (m, 2H), 5.77 and 5.61 (m, 2H), 4.10 (m, 2H), 1.60 to 1.17 (m, 16H), 0.83 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 137.75, 137.35, 133.20, 130.50, 129.50, 129.15, 128.10, 125.55, 72.75, 72.70, 37.35 (2C), 31.85 (2C), 25.20 (2C), 22.70 (2C), 14.15.

(3E)-1-Trimethylsilyl-3-dodecen-1,5-diyn-7-ol ***12***

The same procedure was used as described for **10a**, from (*E*)-1-chloro-1-decen-3-yn-5-ol[11e] (0.53 mmol, 100 mg) and trimethylsilylacetylene (1.07 mmol, 105 mg). Purification by flash chromatography (petroleum ether/AcOEt 7:3) afforded the enediyne **12** in 83% yield (110 mg).

The enediyne **12** may also be obtained by coupling of chloroenyne **5**[11e] with 1-octyn-3-ol according to the same procedure as described for **10a**; yield 72% (875 mg). IR (neat) cm^{-1} 3340, 3030, 2960, 2840, 2220, 1590; ^1H NMR (250 MHz, $CDCl_3$) δ 5.87 (m, 2H), 4.40 t, 1H, J=6.6 Hz), 1.26 (m, 14H),

0.88 (t, 3H, J=6.6 Hz), 0.20 (s, 9H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 121.15, 120.80, 102.65, 100.00, 95.70, 82.65, 62.70, 37.40, 31.20, 24.60, 22.35, 13.80, −0.05; Anal. calcd. for $C_{15}H_{24}OSi$: C, 72.53 H, 9.75 Found: C, 72.41, H, 9.91.

(3E,5E)-1-Trimethylsilyl-3,5-dodecadien-1-yn-7-ol ***13a***

Red-Al (3.2 mmol, 0.95 mL, 3.4 N in toluene) was added slowly (within 10 min) with a syringe to a solution of enediyne **12** (0.2 mmol, 496 mg) in 5 mL of ether at −25°C. The reaction mixture was allowed to warm up to ambient temperature and stirred for an additional 60 min, then hydrolyzed carefully with ice-cooled water. The aqueous layer was extracted with ether (2×10 mL) and the combined organic layers were washed successively with water (2×10 ml), dried over $MgSO_4$ and the solvent was removed *in vacuo*. Purification by flash chromatography (cyclohexane/ether 7:3) furnished the pure dienyne **13a** in 80% yield (400 mg).

The dienyne **13a** may also be obtained by coupling of known chlorodiene[6] **8a** with trimethylsilyl acetylene according to the same procedure as described for **10a**; yield 74% (753 mg). IR (neat) cm^{-1} 3360, 2960–2930, 2120, 1640, 1130; ^{1}H NMR (250 MHz, $CDCl_3$) δ 6.54 (dd, 1H, J=15.6 and 10.8 Hz), 6.16 (dd, 1H, J=15.0 and 10.7 Hz), 5.76 (dd, 1H, J=15.3 and 6.2 Hz), 5.57 (d, 1H, J=15.6 Hz), 4.10 (q, 1H, J=6.4 Hz), 1.65 (s, 1H), 1.50 to 1.40 (m, 2H), 1.30 to 1.20 (m, 6H), 0.80 (t, 3H, J=6.7 Hz), 0.10 (s, 9H);

^{13}C NMR (63 MHz, $CDCl_3$): δ 142.00, 139.40, 129.00, 111.00, 104.20, 97.00, 72.10, 37.05, 31.65, 24.90, 22.50, 13.90, −0.20; CIMS (NH_3) m/e (relative intensity) 233 ($(M+H)^+-H_2O$, 100%); Anal. calcd. for $C_{15}H_{26}OSi$: C, 71.95 H, 10.47 Found: C, 71.44, H, 10.66.

(3E,5E)-3,5-Dodecadien-1-yn-7-ol ***13b***

To the silylated (*E,E*)-dienyne **13a** (2.6 mmol, 650 mg) dissolved in MeOH (5 mL) and THF (6 mL) was added, in 5 min at 20°C, $AgNO_3$ (10 mmol, 1.77 g) dissolved in 10 mL of water and 3 mL of methanol. The temperature rose to 30°C and a precipitate of the silver acetylide was formed. After 30 min, the stirred reaction was treated with a solution of KCN (0.07 mol, 4.55 g) in 5 mL of water. Stirring was continued until the precipitate had dissolved and the reaction mixture was concentrated. Ether was added (20 mL) and the organic layer washed with H_2O (2×10 mL), dried over $MgSO_4$ and the solvent was removed *in vacuo*. Purification by flash chromatography (cyclohexane/ether 6:4) afforded the pure dienyne **13b** in 86% yield (400 mg). IR (neat) cm^{-1} 3330, 3290, 2950–2850, 2090, 1635, 1125; ^{1}H NMR (250 MHz, $CDCl_3$) δ 6.20 (dd, 1H, J=15.6 and 10.4 Hz), 6.20 (dd, 1H, J=15.0 and 10.4), 5.77 (dd, 1H, J=15.0 and 6.2 Hz), 5.30 (dd, 1H, J=15.6 and 2.5 Hz), 4.10 (q, 1H, J=6.2 Hz), 2.97 (d, 1H, J=2.5 Hz), 1.64 (s, 1H), 1.47 (m, 2H), 1.30 to 1.19 (m, 6H), 0.84 (t, 3H, J=6.6 Hz); ^{13}C NMR (63 MHz, $CDCl_3$): δ 142.65, 139.65, 128.60, 109.90, 82.65, 79.55, 71.95, 36.95, 31.60, 24.90, 22.40, 13.90; CIMS (NH_3) m/e (relative intensity) 161 ($(M+H)^+-H_2O$, 100%); Anal. calcd. for $C_{12}H_{18}O$: C, 80.84 H, 10.18 Found: C, 81.04, H, 10.57.

Methyl-(6E,10E,12E)-5,14-dihydroxy-6,10,12-nonadecatrien-8-ynoate ***10b***

To a solution of $Pd(PPh_3)_4$ (0.02 mmol, 22 mg), vinyl iodide **14** (0.387 mmol, 110 mg), piperidine (0.775 mmol, 66 mg) and CuI (0.038 mmol, 7.4 mg) in benzene (5 mL) was added via a syringe pump (addition time 2 h) dienyne **13b** (0.465 mmol, 83 mg). The reaction was stirred at room temperature for 3 h and treated with a saturated solution of NH_4Cl (20 mL). The aqueous layer was extracted with ether (3×10 mL). The combined organic layers were washed with water (10 mL), dried over $MgSO_4$ and concentrated under vacuum. Purification by flash chromatography (cyclohexane/AcOEt 6:4) afforded the trienynol **10b** in 60% yield (77 mg). IR (neat) cm^{-1} 3400, 2980, 2860, 2180, 1735, 1630, 1110; ^{1}H NMR (250 MHz, $CDCl_3$) δ 6.51 (dd, 1H, J=15.4 and 10.8 Hz), 6.20 (dd, 1H, J=15.2 and 10.8 Hz), 6.06 (dd, 1H, J=15.8 and 6.0 Hz), 5.79 (dt, 1H, J=15.7 and 1.3 Hz), 5.73 (dd, 1H, J=15.4 and 6.6 Hz), 5.64 (dd, 1H, J=15.4 and 1.4 Hz), 4.11 (dq, 2H, J=6.0 Hz), 3.61 (s, 3H), 2.28 (t, 2H, J=7.2 Hz), 1.65 (quint, 2H, J=7.2 Hz), 1.51 (q, 2H, J=7.2 Hz), 1.30 to 1.17 (m, 8H), 1.22 (s, 2H), 0.82 (t, 3H, J=6.7 Hz); ^{13}C NMR (63 MHz, $CDCl_3$) δ 174.00, 145.30, 140.85, 139.10, 129.00,

110.95, 109.70, 90.10, 89.35, 71.90, 71.25, 51.40, 37.00, 36.00, 33.55, 31.55, 24.90, 22.40, 20.55, 15.05; CIMS (NH_3) m/e: 335 $(M+H)^+$, 317 $((M+H)^+-H_2O)^+$, 100%).

Ethyl (2S)-2-t-butyldiphenylsilyloxyheptanoate 16

1 M *n*-ButylMgBr in THF (87 mmol, 87 mL) was slowly added to a suspension of CuBr–Me_2S (43.75 mmol, 9.0 g) in THF (170 mL) cooled to −35°C. After stirring for 1 h, (*S*)-ethyl glycidate **15** (35 mmol, 4.06 g) in anhydrous ether (10 mL) was slowly added. After stirring for 1.5 h at the same temperature, the reaction was quenched with a solution of 1/1 sat. aqueous NH_4Cl/10 M NH_4OH (170 mL) and stirred for 1 h until the copper salts were completely dissolved. After extraction with Et_2O (4×100 mL), the organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. After purification by chromatography on a silica gel column (cyclohexane/AcOEt 85:15), the α-hydroxy ester (ethyl (2*S*)-2-hydroxyheptanoate) was isolated as an oil; yield: 86% (5.27 g). $[\alpha]_D^{20}$ −5.3 (c=3.16, MeOH); ee: 99.5% (GC; column: XE 60-*S*-Valine-*S*-α-pea 50 m from Chrompack); IR (neat) cm^{-1} 3400, 1740; ^1H NMR δ 4.10 to 4.20 (m, 1H), 4.08 (q, 2H, J=6.8 Hz), 1.20 to 1.80 (m, 8H), 1.20 (t, 3H, J=7.1 Hz), 0.80 (t, 3H, J=6.8 Hz) ^{13}C NMR δ 175.35 (s), 70.40 (d), 61.40(t), 34.30 (t), 31.40 (t), 24.30 (t), 22.40 (t),14.10 (q), 13.65 (q); CIMS (NH_3) m/e: 192 (M+18, 100%), 174 (M), 136, 102, 94. Anal. calcd. for $C_9H_{18}O_3$: C, 62.04 H, 10.41 Found: C, 62.10 H, 10.36.

t-Butyldiphenylsilylchloride (27mmol, 7.41 g) was added to a solution of α-hydroxy ester previously prepared (25 mmol, 4.35 g) and imidazole (0.125 mol, 8.1 g) in DMF (15 mL). After stirring for 12 h, the mixture was hydrolyzed with 0.1 M HCl and extracted with Et_2O (3×100 mL). The organic phase was washed with a solution of hydrogenocarbonate and dried on $MgSO_4$. The solvents were removed under vacuo and the resulting oil purified by chromatography on silica gel (cyclohexane/AcOEt 93:7); yield: 95% (9.27 g). $[\alpha]_D^{20}$ −26.5 (c=3.16, CH_2Cl_2); IR (neat) cm^{-1} 1745; ^1H NMR δ 7.20 and 7.50 (2m, 10H), 4.05 (t, 1H, J=6.3 Hz), 3.75 (q, 2H, J=7.0 Hz), 1.30 (t, 3H, J=7.1 Hz), 1.10 to 1.30 (m, 8H), 0.96 (s, 9H), 0.68 (t, 3H, J=7.2 Hz); ^{13}C NMR δ 173.25 (s), 135.80 (s), 133.40 (d), 129.65 (d), 127.45 (d), 72.75 (d), 60.30 (t), 35.10 (t), 31.50 (t), 26.90 (s), 24.15 (t), 22.40 (t), 19.40 (q), 14.00 (q), 13.95 (q); CIMS (NH_3) m/e: 430 (M+18), 355, 335 (100%).

(2S)-2-t-Butyldiphenylsilyloxyheptanal 17

1 M Dibal-H solution in CH_2Cl_2 (24 mL) was slowly added to a solution of the ester **16** (20 mmol, 8.24 g) in anhydrous pentane cooled to −65°C. After stirring for 5 h at the same temperature, the mixture was quenched with a mixture of sat. aqueous NH_4Cl/1 M HCl (6 mL/8 mL) and vigorously stirred at room tempetrature for 1 h until formation of a precipitate. After filtration, the organic phase was dried on $MgSO_4$. After removing the solvents under reduced pressure, the crude oil was purified by chromatography on a silica gel column (cyclohexane/AcOEt 93:7); yield: 91% (6.7 g). $[\alpha]_D^{20}$ −1.2 (c=1.85, CH_2Cl_2); IR (neat) cm^{-1} 1730, 1580, 1420; ^1H NMR δ 9.58 (d, 1H, J=1.7 Hz), 7.30 and 7.60 (2m, 10H), 4.00 (dt, 1H, J=1.6 and 6.5 Hz), 1.55 (m, 2H), 1.20 to 1.50 (m, 6H), 1.15 (s, 9H), 0.80 (t, 3H, J=6.9 Hz); ^{13}C NMR δ 203.80 (s), 135.80 (s), 133.15 (d), 129.95 (d), 127.70 (d), 78.15 (d), 32.90 (t), 31.65 (t), 27.05 (s), 23.75 (t), 22.40 (t), 19.40 (q), 13.90 (q); CIMS (NH_3) m/e: 386 (M+18, 100%), 339, 311, 291, 274, 199.

(3R,4S)-3,4-Dihydroxy-1-nonyne 4

1.6 M *n*-butyllithium in hexane (15.6 mL) was slowly added to a solution of trimethylsilyl acetylene (25 mmol, 2.45 g) in THF (15 mL) cooled to −30°C. After stirring for 30 min, anhydrous HMPA (6 mL) was added and the solution was cooled to −78°C before adding a solution of the aldehyde **17** (20 mmol, 7.36 g) in THF (10 mL). After stirring for 1 h, the reaction was quenched with an aqueous saturated solution of NH_4Cl and extracted with Et_2O (3×50 mL). The organic phase was dried on $MgSO_4$. After removing the solvents under reduced pressure, the crude oil was purified by chromatography on a silica gel column (cyclohexane/AcOEt 95:5) to give 7.5 g of a mixture of isomers. Total yield: 81%. The O-protected diols were dissolved in THF (15 mL) and a 1 M solution of tetrabutylammonium fluoride in THF (40 mL) was slowly added at 0°C. After stirring for 1 h, the

mixture was hydrolyzed with water (10 mL) and extracted with diethylether (6×50 mL). The organic phase was dried on $MgSO_4$. After removing the solvents under reduced pressure, the diols were isolated as a mixture of *syn*- and *anti*-isomers (13/87) in 93% yield. The major isomer crystallized slowly and after recrystallisation in hexane, pure *anti*-alcohol **4** was obtained in 69% yield (1.72 g). mp: 63–64°C; $[\alpha]_D^{20}$ −3.1 (c=0.59, CH_2Cl_2); IR (neat) cm^{-1} 3400, 3300, 2100, 1650; ^1H NMR δ 4.33 (dd, 1H, J=2.2 and 3.5 Hz), 3.68 (td, 1H, J=3.5 and 6.0 Hz), 2.51 (d, 1H, J=2.1 Hz), 1.50 (m, 2H), 1.35 (s, 2H), 1.20 (m, 6H), 0.80 (t, 3H, J=6.6 Hz); ^{13}C NMR δ 81.25, 75.05, 75.00, 66.00, 32.55, 31.65, 25.20, 22.50, 11.50; CIMS (NH_3) m/e: 174 (M+18, 100%), 165 (M), 110, 124; Anal. calcd. for $C_9H_{16}O_2$: C, 69.19 H, 10.32 Found: C, 69.28 H, 10.36.

(1E,5R,6S)-1-Chloro-5,6-dihydroxy-undec-1-en-3-yne ***18***

The chloroenyne **18** was obtained from 1-alkynes (3.205 mmol, 500 mg) according to the literature procedure.[11e] Purification by flash chromatography (cyclohexane/AcOEt 65:35) afforded the pure chloroenyne **18** in 76% yield (530 mg). mp: 115–116°C, $[\alpha]_D^{20}$ −21.4 (c=1.3, acetone); IR (neat) cm^{-1} 3380, 3070, 2920, 1580, 920, 840; ^1H NMR (250 MHz, $CDCl_3$) δ 6.40 (d, 1H, J=13.8 Hz), 5.75 (dd, 1H, J=13.6 and 1.9 Hz), 4.27 (dd, 1H, J=3.5 and 1.9 Hz), 3.52 (ddd, 1H, J=6.9, 5.8 and 3.5 Hz), 1.90 (s, 2H), 1.38 (m, 2H), 1.15 (m, 6H), 0.72 (t, 3H J=6.5 Hz); ^{13}C NMR (63 MHz, $CDCl_3$) δ 132.00, 112.95, 89.25, 81.60, 74.10, 66.65, 32.65, 31.70, 25.25, 22.50, 15.20; CIMS (NH_3) m/e (relative intensity) 234 ($(M+NH_4)^+$, 100%, ^{35}Cl), 236 ($(M+NH_4)^+$, ^{37}Cl); Anal. calcd. for $C_{11}H_{17}O_2Cl$: C, 60.97 H, 7.91 Found: C, 61.22, H, 7.87.

(1E,3E,5R,6S)-1-Chloro-5,6-dihydroxy-undeca-1,3-diene ***19***

A suspension of lithium aluminium hydride (8.73 mmol, 332 mg) in anhydrous THF (5 mL) was cooled to −20°C and treated dropwise with a solution of alcohol **18** (1.746 mmol, 378 mg) in 2 mL of THF. After complete addition the cold bath was removed and the mixture was heated on a steam bath for 2 h. The reaction was quenched successively, at −20°C, by the dropwise addition of water (0.4 mL), 15% sodium hydroxide (1 mL) and water (1 mL). After filtration of aluminium hydroxide, evaporation of the solvent and flash chromatography (cyclohexane/AcOEt 6:4) the pure chlorodiene **19** was obtained in 63% yield (240 mg). mp: 97–98°C (hexane–AcOEt); $[\alpha]_D^{20}$ +17.4 (c=1.195, acetone); IR (KBr) cm^{-1} 3300, 2930, 1580, 1470, 980; ^1H NMR (250 MHz, $CDCl_3$) δ 6.19 (ddd, 1H, J=15.2, 11.0 and 1.1 Hz), 6.15 (d, 1H, J=13.0 Hz), 5.66 (dd, 1H, J=15.5 and 6.7 Hz), 4.05 (ddd, 1H, J=6.7, 3.4 and 1.1 Hz), 3.6 (m, 1H), 1.7 to 1.9 (br. s, 2H), 1.2 to 1.4 (m, 8H), 0.8 (t, 3H, J=6.6 Hz); ^{13}C NMR (63 MHz, $CDCl_3$) δ 132.55, 131.55, 128.40, 121.45, 74.90, 74.10, 31.85, 31.55, 25.25, 22.30, 13.75; CIMS (NH_3) m/e (relative intensity) 236 ($M+NH_4^+$), 218 (M^+), 201 (M−18, 100%); Anal. calcd. for $C_{11}H_{19}O_2Cl$: C, 60.40 H, 8.75 Found: C, 60.53, H, 8.82.

(3E,7R,8S)-1-Trimethylsilyl-7,8-dihydroxytridec-3-en-1,5-diyne ***20***

Chloroenyne **5** (1 mmol, 159 mg) and $PdCl_2(PhCN)_2$ (0.07 mmol, 27 mg) were added to a solution of piperidine (20 mmol, 1.7 g) in THF (4 mL). After stirring for 15 min, a solution of diol **4** (1.2 mmol, 187 mg) in THF (1 mL) was added followed by cuprous iodide (0.1 mmol, 19 mg). The mixture was stirred for 2 h and hydrolyzed with a saturated aqueous solution of NH_4Cl (12 mL). After extraction with Et_2O (3×10 mL), the organic phase was dried on $MgSO_4$ and the solvents were removed under reduced pressure. The residual oil was purified by flash-chromatography on a silica gel column (cyclohexane/AcOEt 60:40); yield: 75% (250 mg). $[\alpha]_D^{20}$ +12.9 (c=0.92, CH_2Cl_2); IR (neat) cm^{-1} 3640, 3450, 2900, 2100, 950; ^1H NMR (250 MHz, $CDCl_3$) δ 6.00 (br. s, 2H), 4.50 (d, 1H, J=3.3 Hz), 3.75 (m, 1H), 2.90 (br. s, 2H), 1.50 (m, 2H), 1.30 (m, 6H), 0.90 (t, 3H, J=7 Hz), 0.20 (s, 9H); ^{13}C NMR δ 121.80 (d), 120.80 (d), 102.60 (s), 100.75 (s), 91.85 (s), 84.75 (s), 74.15 (d), 66,75 (d), 32.65 (t), 31.70 (t), 25.25 (t), 22.50 (t), 14.00 (q), −0.30 (s); CIMS (NH_3) m/e: 279 (M+1, 100%), 296 (M+18), 261. Anal. calcd. for $C_{16}H_{26}O_2Si$: C, 69.01 H, 9.41 Found: C, 69.12 H, 9.35.

(3E,5E,7R,8S)-1-Trimethylsilyl-7,8-dihydroxytrideca-3,5-dien-1-yne 21

A solution of the enediyne **20** (0.45 mmol, 125 mg) in anhydrous ether (8 mL) was slowly added at 0°C to a solution of 3.5 M (in toluene) Red-Al (1.35 mmol, 386 µl) in anhydrous ether (5 mL). After stirring for 15 min, the mixture was warmed up to 20°C and stirred for 3 h. After hydrolysis with 1 N hydrochloric acid and extraction with Et_2O (3×10 mL), the organic phase was dried on $MgSO_4$ and the solvents were removed under reduced pressure. The residual oil was purified by flash chromatography on a silica gel column (cyclohexane/AcOEt 6:4); yield: 74% (93 mg). $[\alpha]_D^{20}$ +9.5 (c=0.61, acetone); IR (neat) cm^{-1} 3630, 3450, 1230, 950; ^1H NMR (250 MHz, $CDCl_3$) δ 6.39 (dd, 1H, *J*=10.6 and 15.2 Hz), 6.12 (dd, 1H, J=10.6 and 15.4 Hz), 5.60 (dd, 1H, J=6.8 and 15.3 Hz), 5.42 (d, 1H, J=15.6 Hz), 3.50 (m, 1H), 3.95 (m, 1H), 2.00 to 2.20 (s, 2H), 1.10 to 1.50 (m, 8H), 0.67 (t, 3H, J=6.6 Hz), 0.00 (s, 9H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 141.70 (d), 133.75 (d), 131.75 (d), 111.90 (d), 104.00 (s), 97.75 (s), 75.15 (d), 74.30 (d), 32.00 (t), 31.75 (t), 25.50 (t), 22.50 (t), 14.00 (q), −0.15 (s); CIMS (NH_3) m/e: 298 (M+18), 281 (M+1), 261 (100%), 247, 191, 179.

(3E,5E,7R,8S)-7,8-Dihydroxytrideca-3,5-dien-1-yne 2

The same procedure was used as decribed for **13b**, from silylated dienyne **21** (0.196 mmol, 55 mg). Purification by flash chromatography (cyclohexane/AcOEt 6:4) afforded the terminal dienyne **2** in 98% yield (40 mg). $[\alpha]_D^{20}$ +16 (c=0.82, acetone); IR (neat) cm^{-1} 3640, 3450, 2950, 2850, 1625, 1120; ^1H NMR (250 MHz, $CDCl_3$) δ 6.64 (dd, 1H, J=15.6 and 10.8 Hz), 6.30 (dd, 1H, J=15.4 and 10.4 Hz), 5.85 (dd, 1H, J=15.3 and 6.6 Hz), 5.6 (dd, 1H, J=15.5 and 2.3 Hz), 4.1 (dd, 1H, J=6.5 and 3.6 Hz), 3.65 (m, 1H), 2.95 (d, 1H, J=2.3 Hz), 2.2 to 1.95 (br. s, 2H), 1.4 to 1.1 (m, 8H), 0.8 (t, 3H, J=6.6 Hz); ^{13}C NMR (63 MHz, $CDCl_3$) δ 142.40, 134.10, 131.45, 110.75, 82.55, 80.05, 75.05, 74.30, 31.95, 31.75, 25.50, 22.55, 14.00; CIMS (NH_3) m/e (relative intensity) 228 (M+18, 100%), 218 (M^+), 191, 110.

Methyl (5S,6E,10E,12E,14R,15S)-5,14,15-trihydroxy-6,10,12-eicosatrien-8-ynoate 22

The same procedure was used as described for **10b**, from dienyne **2** (0.418 mmol, 87 mg) and vinyl iodide **3** (0.348 mmol, 100 mg). Purification by flash chromatography (cyclohexane/AcOEt 6:4) afforded the trienyne **22** in 55% yield[20] (70 mg). $[\alpha]_D^{20}$ +12.2 (c=0.36, $CHCl_3$) Lit: $[\alpha]_D^{20}$ +11.9 (c=0.41, $CHCl_3$);[21] ^1H NMR (250 MHz, $CDCl_3$) δ 6.55 (dd, 1H, J=15.4 and 10.8 Hz), 6.31 (dd, 1H, J=14.9 and 10.8 Hz), 6.10 (dd, 1H, J=15.0 and 6.0 Hz), 5.87 (d, 1H, J=15.0 Hz), 5.80 (dd, 1H, J=15.0 and 6.8 Hz), 5.72 (dd, 1H, J=15.0 and 2.1 Hz), 4.15 (m, 2H), 3.75 (m, 1H), 3.68 (s, 3H), 2.34 (t, 2H, J=7.3 Hz), 2.05 (d, 1H, J=4.7 Hz), 1.92 (d, 1H, J=4.8 Hz), 1.67 (q, 2H, J=7.2 Hz), 1.40 (m, 2H), 1.22 (m, 9H), 0.90, (t, 3H, J=6.6 Hz); ^{13}C NMR (63 MHz, $CDCl_3$) δ 174.10, 145.15, 140.60, 133.40, 131.95, 111.95, 110.15, 90.50, 89.55, 75.20, 74.35, 71.70, 51.65, 36.10, 33.65, 32.00, 31.75, 25.50, 22.55, 20.55, 14.00; CIMS (NH_3) m/e (relative intensity) 382 (M+18), 364 (M^+), 347 (100%).

Methyl (5S,6E,8Z,10E,12E,14R,15S)-5,14,15-trihydroxy-6,8,10,12-eicosatetraenoate 1b

A solution of the trienyne **22** (0.16 mmol, 58 mg) in MeOH (6 mL) was added to a suspension of activated zinc[9] (1 g) in 1/1 MeOH/H_2O (10 mL). After stirring for 17 h in the dark, the suspension was filtered and the solid washed with MeOH. The combined solutions were evaporated under reduced pressure and the residue was dissolved in Et_2O (15 mL) dried on $MgSO_4$ and evaporated under reduced pressure. The residual oil was purified by flash chromatography on a silica gel column (pentane/AcOEt 40:60) to give 42 mg of the pure compound **1b**; yield: 72%. $[\alpha]_D^{20}$ +18 (c=2.1, $CHCl_3$) Lit: $[\alpha]_D^{20}$ +19.2 (c=1.16, $CHCl_3$)[4c] ^1H NMR (400 MHz, $CDCl_3$) δ 6.74 (m, 2H), 6.42 (dd, 1H, J=10.6 and 15.0 Hz), 6.30 (dd, 1H, J=10.5 and 14.8 Hz), 6.05 (m, 2H), 5.85 (dd, 1H, J=7.0 and 15.0 Hz), 5.79 (dd, 1H, J=6.7 and 15.0 Hz), 4.26 (q, 1H, J=6.5 Hz), 3.75 (m, 1H), 4.00 (m, 1H), 3.71 (s, 3H), 2.40 (t, 2H, J=7.2 Hz), 2.13 (br. s, 1H), 2.04 (br. s, 1H), 1.78 (m, 2H), 1.65 (m, 2H), 1.52 (br. s, 1H), 1.44 (m, 2H), 1.33 (m, 6H), 0.92 (t, 3H, J=6.5 Hz); ^{13}C NMR δ 174.10 (s), 137.10 (d), 133.00 (d), 132.90 (d), 131.60 (d), 129.55 (d), 129.25 (d), 128.50 (d), 125.60 (d), 75.50 (d), 74.40 (d), 72.05 (d), 51.60

(t), 36.50 (t), 33.75 (t), 32.10 (t), 31.80 (t), 25.50 (t), 22.55 (q), 20.75 (t), 14.0 (q); CIMS (NH_3) m/e (relative intensity) 384 (M+18), 367 (M+1), 349 (100%), 331.

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