First Stereoselective Total Synthesis of Gallicynoic Acids G and H

by **Palakodety Radha Krishna*** and **Kadimi Anitha**

D-211, Discovery Laboratory, Organic Chemistry Division-III, Indian Institute of Chemical Technology, Hyderabad 500 607, India
(phone: +91-40-27193158; fax: +91-40-27160387; e-mail: prkgenius@iict.res.in)

A stereoselective convergent total synthesis of two acetylenic acids, gallicynoic acid G (**1**) and H (**2**), is reported, involving asymmetric reduction of alkynones **3** and **4**, respectively, with the *Corey–Bakshi–Sibata* (*CBS*) catalyst as a key step (*Scheme 3*), **3** and **4** being obtained from a common intermediate, the chiral alkynol **12** (*Scheme 2*).

Introduction. – Acetylenic acids are widespread in nature, are found in many organisms, and are ubiquitous in plants of the Compositae/Asteraceae and Umbelliferae/Apiaceae and the fungi of the Basidiomycete group [1][2]. More than 600 naturally occurring acetylenic and polyacetylenic acids have been isolated from different sources. Some of them have shown a variety of biological activities such as cytotoxic, antimicrobial, enzyme-inhibitory, and anti-HIV activities [2–8]. Recently, gallicynoic acids G (**1**) and H (**2**) were isolated from a culture of the basidiomycete *Coriolopsis gallica* [9]. Our interest in chiral propynyl alcohols and allyl propynyl alcohols dates back in time and recently led to their synthesis *via Baylis–Hillman* reaction [10] of corresponding propynals. These multifunctional products are versatile synthons in the synthesis of bioactive natural products [11]. Taking this interest further, we embarked on the synthesis of newly isolated gallicynoic acids, and the results are disclosed herein.

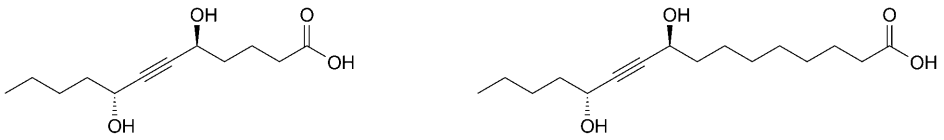
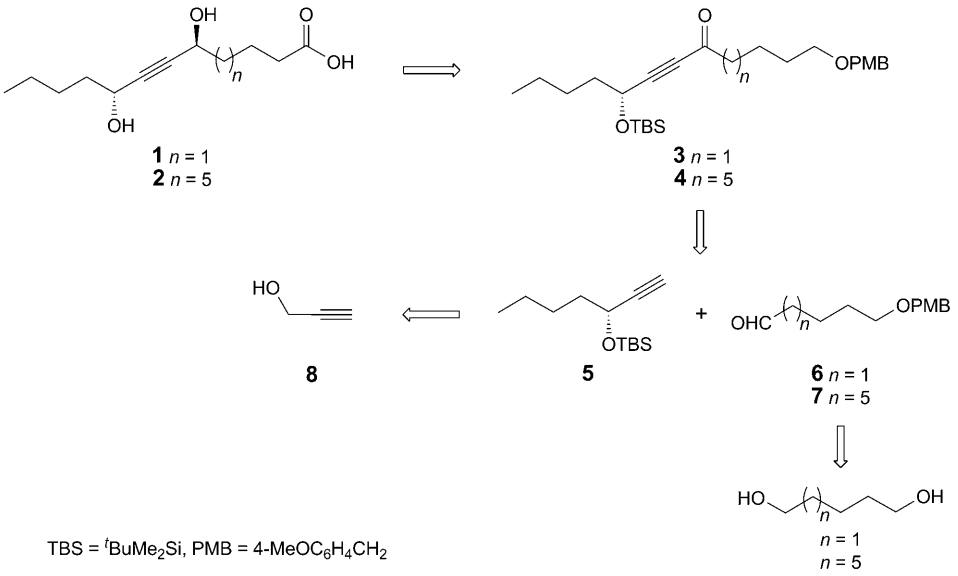


Figure. *Structures of gallicynoic acids G* (**1**) *and H* (**2**)

Scheme 1 outlines our retrosynthetic strategy for the synthesis of gallicynoic acids **1** and **2**. We used the protected alkynol derivative **5** [12c] as a common intermediate for the construction of the alkyne part of **1** and **2**. The basic C-atom skeletons with the required configuration could be achieved *via* the asymmetric reduction of alkynones **3** and **4**, respectively. These alkynones in turn could be obtained through a convergent synthesis from the nucleophilic addition reaction of alkynol derivative **5** with aldehydes **6** [13] and **7** [14], respectively, followed by the oxidation of the resultant OH group. The

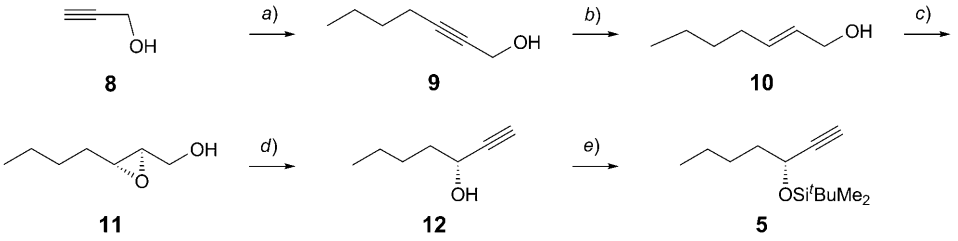
Scheme 1. *Retrosynthetic Analysis of Gallicynoic Acids G* (**1**) *and H* (**2**)



enantiomerically pure alkynol **12** [12b][12d] was accessed by a modified route *via* the *Sharpless* asymmetric epoxidation protocol, starting from prop-2-yn-1-ol (**8**).

Results and Discussion. – The synthesis of the gallicynoic acids G (**1**) and H (**2**) started from the commercially available prop-2-yn-1-ol (= propargyl alcohol; **8**). Butylation of **8** (*Scheme 2*) with BuBr in liquid NH_3 and Li at $-33°$ afforded **9** in 75% yield [15]. Reduction of **9** with $LiAlH_4$ [15b] gave stereochemically pure (*E*)-alkenol **10** in 90% yield. *Sharpless* asymmetric epoxidation of **10** ((−)-diisopropyl tartrate (DIPT), $(^iPrO)_4Ti$, cumene hydroperoxide (CHP), $-20°$) furnished (2*R*,3*R*)-oxiranemethanol **11** [16], which on subsequent reaction with Ph_3P in CCl_4 in the presence of

Scheme 2. *Synthesis of Fragment* **5**

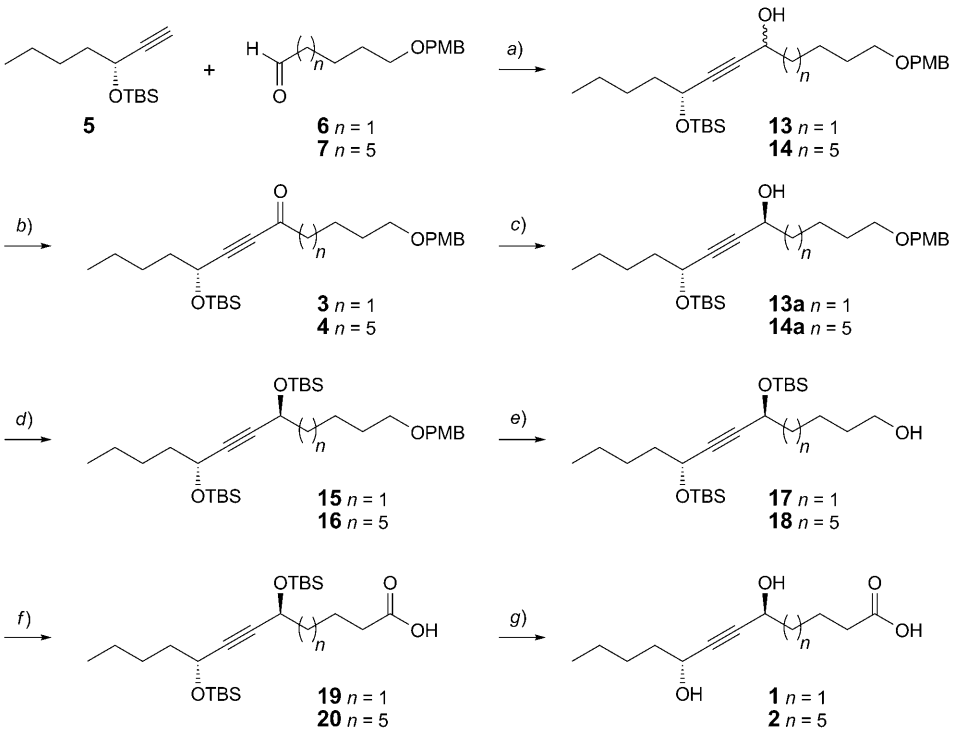


a) Li, liq. NH_3, $Fe(NO_3)_3$, HMPA, THF, BuBr, $-33°$, 6 h; 75%. *b*) $LiAlH_4$, THF, 0° to reflux, 5 h; 90%. *c*) (−)-Diisopropyl tartrate (DIPT), $(^iPrO)_4Ti$, cumene hydroperoxide (= 1-methyl-1-phenylethyl hydroperoxide; CHP), CH_2Cl_2, $-20°$, 4–5 h; 90%. *d*) 1. Ph_3P, $NaHCO_3$ (cat.), CCl_4, reflux, 2 h; 84%. 2. BuLi, $(^iPr)_2NH$, THF, $-40°$, 1 h; 75%. *e*) $^tBuMe_2SiCl$, 1*H*-imidazole, CH_2Cl_2, 0°–r.t., 2 h; 78%.

$NaHCO_3$ (cat.) under reflux gave the (chloromethyl)oxirane in 84% yield. The fragmentation of the latter on treatment with lithium diisopropylamide (LDA) [12b] at $-78°$ to $-40°$ afforded the chiral alkynol **12** [12] in 75% yield. Further, the free OH group of **12** was protected as its (*tert*-butyl)dimethylsilyl ether **5** (^{t}BuMe$_2$SiCl, 1*H*-imidazole, CH_2Cl_2, 0°, r.t., 2 h; 78%).

The construction of the basic C-atom skeleton of the gallicynoic acids **1** and **2** (*Scheme 3*) was achieved by the alkynylation reaction [17] of the known aldehyde **6** or **7**, respectively, with the (silyloxy)alkyne **5**. The alkynol **13** (or **14**, resp.) was obtained as a mixture of diastereoisomers. An asymmetric alkynylation reaction of **6** [12] with **5** under *Carreira* conditions [18] was not pursued due to poor yield of the product. Thus, to achieve the (*S*)-configured alkynols in an optically pure form, we resorted to an oxidation–reduction protocol: Alkynol **13** (or **14**, resp.) was oxidized to alkynone **3** (or **4**, resp.) in the presence of 2-iodoxybenzoic acid (IBX). The ^{13}C-NMR spectrum of **3**

Scheme 3



TBS = ^{t}BuMe$_2$Si, PMB = 4-MeOC$_6$H$_4$CH$_2$

a) BuLi, THF, $-78°$, 3 h; 75%. *b*) IBX, CH_2Cl_2, DMSO, 0°–r.t., 2 h; 79%. *c*) (*S*)-methyloxazaborolidine *CBS* catalyst, $BH_3 \cdot SMe_2$, THF, $-30°$, 2–3 h; 94%. *d*) ^{t}BuMe$_2$SiCl, 1*H*-imidazole, CH_2Cl_2, 0°–r.t., 2 h; 83%. *e*) DDQ, CH_2Cl_2/H_2O 19:1, 0°, 30 min; 76%. *f*) 1. $(COCl)_2$, DMSO, Et_3N, $-78°$, 1 h; 85%. 2. $NaClO_2$, $NaH_2PO_4 \cdot 2\,H_2O$, 2-methylbut-2-ene, ^{t}BuOH/H_2O 3:1, 0°–r.t., 12 h; 85%. *g*) HF (40%), MeCN, 0°–r.t., 2 h; 61%.

showed a signal due to the C=O group at δ(C) 187.4 [19b]. Then, the (*S*)-configured alkynol **13a** (or **14a**, resp.) was obtained *via* asymmetric reduction [19] of **3** (or **4**, resp.) in the presence of (*S*)-*Corey–Bakshi–Shibata* catalyst ((*S*)-*CBS* catalyst = (3a*S*)-tetrahydro-1-methyl-3,3-diphenyl-1*H*,3*H*-pyrrolo[1,2-*c*][1,3,2]oxazaborole), in 94% yield and in 90% de. The diastereoisomer purity of product **13a** (or **14a**, resp.) was determined by chiral HPLC analysis. The free OH group was protected as its silyl ether **15** (or **16**, resp.) (^{t}BuMe$_2$SiCl, 1*H*-imidazole, CH_2Cl_2, 0° to r.t.). The deprotection of the 4-methoxybenzyl (PMB) ether group was carried out under conventional reaction conditions (DDQ (=4,5-dichloro-3,6-dioxocyclohexa-1,4-diene-1,2-dicarbonitrile), CH_2Cl_2/H_2O 19:1, r.t.). The oxidation of the resultant primary alcohol **17** (or **18**, resp.) under *Swern* conditions furnished the aldehyde, which on subsequent oxidation ($NaClO_2$, $NaH_2PO_4 \cdot 2\,H_2O$, 2-methylbut-2-ene) [20] afforded the ^{t}BuMe$_2$SiCl-protected gallicyanoic acid **19** (or **20**, resp.) in 85% yield. The formation of **19** and **20** was confirmed by their spectroscopic data. Thus, the ^{1}H-NMR spectrum of **19** showed a *t* for the CH$_2$(α) group at δ(H) 2.37 and the ^{13}C-NMR spectrum a C=O signal at δ(C) 179.5. Finally, the deprotection of the silyl ether moieties of **19** and **20** with HF (40% aq. soln.) in MeCN at 0° for 2 h afforded **1** and **2** in 5.4 and 3.7% overall yield (from **8**), respectively. The $[\alpha]_D^{25}$, ^{1}H- and ^{13}C-NMR data of the synthesized acids **1** and **2** matched the reported data of gallicynoic acid G and H, respectively.

Conclusions. – The stereoselective synthesis of gallicynoic acids G (**1**) and H (**2**) was achieved *via* a common intermediate, the chiral alkynol **12**, by means of a convergent synthesis involving asymmetric reduction of alkynone **3** and **4**, respectively, with the *CBS* reagent as the key step.

One of the authors (*K. A.*) thanks the *CSIR*, New Delhi, for the financial support in the form of a fellowship.

Experimental Part

General. Reactions were carried out under N_2 in anh. solvents such as CH_2Cl_2 and THF (TLC monitoring). Org. soln. were dried (Na_2SO_4) and concentrated below 40°. Yields refer to chromatographically and spectroscopically (^{1}H- and ^{13}C-NMR) homogeneous material. Air-sensitive reagents were transferred by syringe or double-ended needle. TLC: *Merck 60 F_{254}* SiO_2 plates; detection by spraying with naphthalen-1-ol followed by heating. Column chromatography (CC): silica gel (SiO_2, 60–120 mesh; *Acme Synthetic Chemicals, Mumbai, India*). HPLC: *Shimadzu Lc-20A*; *Chiral-pak-IC* column; t_R in min. Optical rotations: *Jasco-DIP-300* digital polarimeter; at 25°. IR Spectra: *Perkin-Elmer-IR-683* spectrophotometer; NaCl optics; $\tilde{\nu}$ in cm^{-1}. ^{1}H- and ^{13}C-NMR spectra: *Bruker-Avance* (^{1}H and ^{13}C) 300 MHz and *Inova* 500 MHz spectrometers; at 300 or 500 (^{1}H) amd 75 MHz (^{13}C); 7–10 mM soln. in $CDCl_3$; δ in ppm rel. to Me_4Si as internal standard, *J* in Hz. MS: *Finnigan-Mat-1210* double-focusing mass spectrometers operating at a direct inletsystem, ESI-MS with an ion-trap mass spectrometer; in *m*/*z*.

Hept-2-yn-1-ol (**9**) [14b]. To a stirred soln. of Li (0.005 mg) in liq. NH_3 (60 ml) under N_2 at −33° were added a few crystals of $Fe(NO_3)_3 \cdot 9\,H_2O$, followed, over 30 min, by finely cut Li (1.24 g, 178.57 mmol) in small portions. After the mixture turned to gray, it was stirred for another 30 min. Distilled prop-2-yn-1-ol (**8**; 5.0 g, 89.28 mmol) in dry THF (40 ml) was added in 30 min, followed by stirring for 90 min. BuBr (9.6 ml, 89.28 mmol) in dry THF (40 ml) was added within 30 min. The resulting mixture was stirred for 5 h at −33°. Then, NH_3 was allowed to evaporate overnight. After slow addition of sat. aq. NH_4Cl soln. (50 ml), the mixture was extracted with AcOEt (3 × 50 ml), the combined org.

extract washed with brine (100 ml), dried (Na_2SO_4), and concentrated, and the residue purified by CC (hexane/AcOEt 98:2): **9** (7.5 g, 75%). Pale-yellow liquid.

*(3*R*)-Hept-1-yn-3-ol* (**12**) [12b]. A stirred soln. of **11** [16] (4.0 g, 30.7 mmol), Ph_3P (8.0 g, 30.7 mmol), and $NaHCO_3$ (0.4 g) in CCl_4 (30 ml) was heated under reflux for 3 h. The solvent was evaporated and the residue purified by CC (hexane/AcOEt 98:2) to afford the corresponding (chloromethyl)oxirane (2.9 g, 84%) as a colorless liquid, which was purified and used for the next step without characterization. To freshly prepared LDA (prepared from $^i Pr_2NH$ (8.2 ml, 58.5 mmol) and BuLi (23.4 ml, 58.5 mmol; 2.5M in hexane)) in THF (30 ml), a soln. of the (chloromethyl)oxirane (2.9 g, 19.5 mmol) in THF (15 ml) was added at $-40°$. After 45 min, the reaction was quenched with sat. aq. NH_4Cl soln. (20 ml) and the mixture diluted with AcOEt. The org. layer was washed with brine (50 ml), dried (Na_2SO_4), and concentrated and the residue purified by CC (hexane/AcOEt 96:4): **12** (1.65 g, 75%). Yellow liquid.

(tert-*Butyl*)*{[(1*R*)-1-butylprop-2-yn-1-yl]oxy}dimethylsilane* (**5**). To a stirred soln. of **12** [12b] (3.8 g, 16.8 mmol) in CH_2Cl_2 (40 ml), 1*H*-imidazole (3.4 g, 50.4 mmol) was added at 0° and the mixture stirred for 5 min. Then $^t BuMe_2SiCl$ (2.7 g, 18.4 mmol) was added, and the stirring was continued for 2 h at r.t. The mixture was diluted with CH_2Cl_2 (20 ml), the org. layer washed with H_2O (60 ml) and brine (10 ml), the combined org. layer concentrated, and the residue purified by CC (hexane/AcOEt 98:2): **5** (0.27 g, 79%). Colorless liquid. $[\alpha]_D^{25} = +81.65$ ($c = 2.0$, $CHCl_3$). IR (KBr): 3324, 2964, 2126, 1225, 839. ^{1}H-NMR (300 MHz, $CDCl_3$): 4.27 (*dt*, $J = 6.4, 1.8, 1$ H); 2.27 (*d*, $J = 2.2, 1$ H); 1.67–1.60 (*m*, 2 H); 1.44–1.22 (*m*, 4 H); 0.93–0.85 (*m*, 12 H); 0.09 (*d*, $J = 7.9$, 6 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 85.7; 75.5; 71.8; 38.2; 29.6; 27.2; 25.7; 22.3; 14.1; −5.0. ESI-MS: 249 ($[M + Na]^+$).

*(8*R*)-8-{[(*tert*-Butyl)dimethylsilyl]oxy}-1-[(4-methoxybenzyl)oxy]dodec-6-yn-5-ol* (**13**). BuLi (1.0 ml, 2.65 mmol; 2.5M in hexane) was added dropwise to a soln. of **5** (0.60 g, 2.65 mmol) in anh. THF (5 ml) at −78°. The mixture was allowed to be stirred for 30 min, then a soln. of aldehyde **6** [13] (0.47 g, 2.12 mmol) in dry THF (5 ml) was added dropwise. The resulting mixture was stirred for 3 h at −78°. The mixture was poured into sat. aq. NH_4Cl soln. (10 ml) and extracted with AcOEt (3 × 25 ml), the combined org. extract washed with brine (50 ml), dried (Na_2SO_4), and concentrated, and the residue was purified by CC (hexane/AcOEt 96:4): **13** (0.89 g, 75%) as a mixture of diastereoisomers. Pale-yellow liquid. $[\alpha]_D^{25} = +52.34$ ($c = 0.35$, $CHCl_3$). IR (KBr): 3419, 2948, 2933, 2858, 1513, 1462, 1359, 1249, 1089, 837, 777. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.20 (*d*, $J(A,B) = 8.4$, 2 H); 6.82 (*d*, $J(A',B') = 8.6$, 2 H); 4.39 (*s*, 2 H); 4.34–4.30 (*m*, 2 H); 3.78 (*s*, 3 H); 3.40 (*t*, $J = 6.2$, 2 H); 1.71–1.48 (*m*, 6 H); 1.39–1.25 (*m*, 6 H); 0.93–0.88 (*m*, 12 H); 0.08 (*d*, $J = 6.4$, 6 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 159.1; 130.4; 129.3; 113.7; 86.6; 84.6; 72.5; 69.7; 62.8; 62.2; 55.2; 38.3; 37.3; 29.31; 27.2; 25.7; 22.9; 18.1; 13.9; −4.5; −5.0. ESI-MS: 471 ($[M + Na]^+$).

*(8*R*)-8-{[(*tert*-Butyl)dimethylsilyl]oxy}-1-[(4-methoxybenzyl)oxy]dodec-6-yn-5-one* (**3**). To a stirred soln. of IBX (0.43 g, 1.56 mmol) in DMSO (1 ml) under N_2, **13** (0.35 g, 0.78 mmol) in anh. CH_2Cl_2 (4 ml) was added at 0°, and the mixture was stirred for 2 h. After dilution with CH_2Cl_2 (20 ml), the mixture was filtered through a pad of *Celite*, the filtrate washed with sat. aq. $NaHCO_3$ soln. (20 ml), dried (Na_2SO_4), and concentrated, and the residue purified by CC (hexane/AcOEt 98:2): **3** (0.27 g, 79%). Colorless liquid. $[\alpha]_D^{25} = +47.06$ ($c = 1.13$, $CHCl_3$). IR (KBr): 2953, 2859, 2209, 1718, 1678, 1513, 1464, 1358, 1251, 1089, 837, 778. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.20 (*d*, $J(A,B) = 8.3$, 2 H); 6.80 (*d*, $J(A',B') = 8.8$, 2 H); 4.45 (*t*, $J = 6.2$, 1 H); 4.38 (*s*, 2 H); 3.79 (*s*, 3 H); 3.41 (*t*, $J = 6.2$, 3 H); 2.54 (*t*, $J = 7.2$, 2 H); 1.77–1.67 (*m*, 4 H); 1.63–1.57 (*m*, 2 H); 1.43–1.32 (*m*, 4 H); 0.94–0.91 (*m*, 12 H); 0.13 (*d*, $J = 5.6$, 6 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 187.4; 159.0; 131.5; 129.1; 113.6; 93.4; 82.9; 72.4; 68.3; 62.6; 55.1; 45.0; 37.4; 28.8; 27.3; 25.6; 22.1; 20.6; 13.9; −4.6; −5.1. ESI-MS: 469 ($[M + Na]^+$).

*(5*S*,8*R*)-8-{[(*tert*-Butyl)dimethylsilyl]oxy}-1-[(4-methoxybenzyl)oxy]dodec-6-yn-5-ol* (**13a**). Ketone **3** (0.25 g, 0.56 mmol) was dissolved in dry THF (3 ml) and cooled to −30°. To this soln., (*S*)-*CBS* reagent (0.35 ml, 1.17 mmol) was added, and then $BH_3 \cdot SMe_2$ (0.26 ml, 2.8 mmol) was added dropwise over 5 min. The resulting mixture was stirred for 1.5 h at −30°. The reaction was quenched by addition of MeOH (0.3 ml) and stirring was continued for another 10 min. After the addition of NH_4Cl soln., the mixture was extracted with Et_2O (3 × 7 ml), the combined org. phase dried (Na_2SO_4) and concentrated, and the residue purified by CC (hexane/AcOEt 98:2): **13a** (0.23 g, 94%). Colorless liquid. HPLC (*Chiral Pak-IC*, 3% ^{i}PrOH/hexane, flow rate 1 ml/min, 210 nm): t_R (major) 9.922, t_R (minor) 10.809. $[\alpha]_D^{25} =$

+35.07 ($c = 0.58$, $CHCl_3$). IR (KBr): 3419, 2948, 2933, 2858, 1513, 1462, 1359, 1249, 1089, 838, 776. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.20 (d, $J(A,B) = 8.6$, 2 H); 6.8 (d, $J(A',B') = 8.6$, 2 H); 4.39 (s, 2 H); 4.32 (t, $J = 6.2$, 2 H); 3.78 (s, 3 H); 3.40 (t, $J = 6.2$, 2 H); 1.71–1.48 (m, 6 H); 1.39–1.25 (m, 6 H); 0.93–0.88 (m, 12 H); 0.08 (d, $J = 6.4$, 6 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 159.1; 130.6; 129.2; 113.7; 86.7; 84.7; 72.5; 69.9; 62.9; 62.3; 55.2; 38.3; 37.5; 29.3; 27.3; 25.8; 22.3; 18.1; 13.9; −4.5; −5.0. ESI-MS: 471 ($[M + Na]^+$). HR-MS: 471.2913 ($[M + Na]^+$, $C_{26}H_{44}NaO_4Si^+$; calc. 471.2906).

*1,1′-{[(1*R*,4*S*)-1-Butyl-4-{4-[(4-methoxybenzyl)oxy]butyl}but-2-yne-1,4-diyl]bis(oxy)}bis[(*tert*-butyl)dimethylsilane]* (**15**). To a stirred soln. of **13a** (0.22 g, 0.49 mmol) in CH_2Cl_2 (4.0 ml), 1*H*-imidazole (0.99 g, 1.47 mmol) was added at 0° and stirred for 15 min. Then, ^{t}BuMe$_2$SiCl (0.08 g, 0.58 mmol) was added and the mixture stirred for 2 h at r.t. The mixture was diluted with CH_2Cl_2 (4 ml), the org. layer washed with H_2O (10 ml) and brine (10 ml), the combined org. phase dried (Na_2SO_4) and concentrated, and the residue purified by CC (hexane/AcOEt 98:2): **17** (0.23 g, 83%). Colorless liquid. $[\alpha]_D^{25} = +40.03$ ($c = 1.71$, $CHCl_3$). IR (KBr): 2972, 2953, 2859, 2209, 1606, 1512, 1464, 1254, 1085, 838, 776. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.17 (d, $J(A,B) = 8.6$, 2 H); 6.78 (d, $J(A',B') = 8.6$, 2 H); 4.35 (s, 2 H); 4.28 (t, $J = 6.4$, 2 H); 3.75 (s, 3 H); 3.36 (t, $J = 6.2$, 2 H); 1.65–1.22 (m, 12 H); 0.90–0.83 (m, 21 H); 0.08–0.03 (m, 12 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 159.1; 130.8; 129.1; 113.8; 85.7; 85.3; 72.5; 70.0; 62.9; 62.8; 55.2; 38.4; 38.3; 29.4; 27.4; 25.7; 22.3; 21.9; 18.2; 13.9; −4.4; −5.0. ESI-MS: 562 ($[M + H]^+$).

*(5*S*,8*R*)-5,8-Bis{[(*tert*-Butyl)dimethylsilyl]oxy}dodec-6-yn-1-ol* (**17**). To a soln. of **15** (0.20 g, 0.35 mmol) in CH_2Cl_2/H_2O 19:1 (5 ml), DDQ (0.96 g, 0.42 mmol) was added at 0° and stirred for 30 min at 0°. The mixture was quenched by the addition of sat. $NaHCO_3$ soln. (5 ml) and extracted with CH_2Cl_2 (3 × 10 ml). The combined org. phase was washed with brine (20 ml), dried (Na_2SO_4), and concentrated and the residue purified by CC (hexane/AcOEt 95:5): **17** (0.12 g, 76%). Colorless liquid. $[\alpha]_D^{25} = +19.58$ ($c = 0.55$, $CHCl_3$). IR (KBr): 3417, 2946, 2931, 2857, 1609, 1464, 1358, 1252, 1086, 778. ^{1}H-NMR (300 MHz, $CDCl_3$): 4.38–4.31 (q, $J = 6.7$, 2 H); 3.64 (t, $J = 6.7$, 2 H); 1.71–1.25 (m, 12 H); 0.92–0.88 (m, 21 H); 0.12–0.06 (m, 12 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 84.9; 85.5; 62.5; 38.0; 32.1; 29.2; 27.2; 22.0; 21.0; 18.2; −4.5; −5.5. ESI-MS: 466 ($[M + Na]^+$). HR-MS: 443.3384 ($[M + H]^+$, $C_{24}H_{51}O_3Si_2^+$; calc. 443.3376).

*(5*S*,8*R*)-5,8-Bis{[(*tert*-Butyl)dimethylsilyl]oxy}dodec-6-ynoic Acid* (**19**). To a stirred soln. of $(COCl)_2$ (0.02 ml, 0.33 mmol) in dry CH_2Cl_2 (2 ml), DMSO (0.04 ml, 0.67 mmol) was added at −78° and stirred for 30 min at −78°, followed by the addition of **17** (0.10 g, 0.22 mmol) in CH_2Cl_2 (1.5 ml). The mixture was stirred for 1 h at −78°, Et_3N (0.18 ml, 1.35 mmol) was added at −78°, and stirring was continued for another 15 min. The mixture was poured into H_2O and extracted with CH_2Cl_2 (2 × 10 ml). The combined org. phase was washed with brine (20 ml), dried (Na_2SO_4), and concentrated: aldehyde (0.08 g, 89%) as a pale yellow syrup with was used for the next reaction without purification and characterization. To this aldehyde (0.08 g, 0.19 mmol) in *t*-BuOH/2-methylbut-2-ene 3:1 (2.5 ml), $NaClO_2$ (0.03 g, 0.38 mmol) and $NaH_2PO_4 \cdot 2\ H_2O$ (0.06 g, 0.38 mmol) dissolved in a minimum amount of H_2O were added at 0° and allowed to be stirred for 6 h at r.t. The solvent was evaporated, the residue dissolved in H_2O (10 ml) and extracted with AcOEt (2 × 10 ml), the combined org. phase washed with brine (15 ml), dried (Na_2SO_4), and concentrated, and the residue purified by CC (hexane/AcOEt 94:6): **19** (0.07 g, 85%). Colorless liquid. $[\alpha]_D^{25} = +17.43$ ($c = 1.36$, $CHCl_3$). IR (KBr): 3425, 2933, 2922, 2854, 1718, 1456, 1408, 1247, 1065. ^{1}H-NMR (300 MHz, $CDCl_3$): 4.37 (t, $J = 6.0$, 1 H); 4.31 (t, $J = 6.0$, 1 H); 2.37 (t, $J = 7.5$, 2 H); 1.84–1.58 (m, 6 H); 1.40–1.25 (m, 4 H); 0.92–0.88 (m, 21 H); 0.11–0.10 (m, 12 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 179.5; 85.6; 85.5; 62.9; 38.6; 38.3; 33.9; 29.0; 25.8; 22.3; 18.2; 14.2; −4.4; −4.9. ESI-MS: 479 ($[M + Na]^+$). HR-MS: 479.3007 ($[M + Na]^+$, $C_{24}H_{48}O_4NaSi_2^+$; calc. 479.2988).

*(5*S*,8*R*)-5,8-Dihydroxydodec-6-ynoic Acid* (**1**). To a stirred soln. of **19** (0.05, 0.12 mmol) in MeCN (2 ml), 40% aq. HF soln. (0.05 ml) was added at 0° and stirred for 2 h at r.t. The mixture was quenched by the addition of sat. $NaHCO_3$ soln. (5 ml) and extracted with AcOEt (3 × 10 ml), the combined org. phase washed with brine (15 ml), dried (Na_2SO_4), and concentrated, and the residue purified by CC (hexane/AcOEt 60:40): **1** (0.017 g, 61%). Colorless liquid. $[\alpha]_D^{25} = -0.9$ ($c = 0.185$, MeOH). IR (KBr): 3418, 2924, 2935, 2855, 2020, 1720, 1539, 1458, 1409, 1242, 1075. ^{1}H-NMR (500 MHz, CD_3OD): 4.36 (t, $J = 5.8$, 1 H); 4.31 (t, $J = 6.8$, 1 H); 2.36 (t, $J = 6.8$, 2 H); 1.78–1.57 (m, 6 H); 1.38–1.26 (m, 4 H); 0.85 (t, $J = 6.8$,

3 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 177.4; 86.7; 86.1; 62.8; 62.5; 38.7; 38.3; 34.6; 28.6; 23.5; 22.0; 14.4. ESI-MS: 251 ($[M+Na]^+$). HR-MS: 251.1263 ($[M+Na]^+$, $C_{12}H_{20}NaO_4^+$; calc. 251.1259).

*(5*R*)-5-{[(*tert*-Butyl)dimethylsilyl]oxy}-16-[(4-methoxybenzyl)oxy]hexadec-6-yn-8-ol* (**14**). As described for **13**, from **5** (0.60 g, 3.54 mmol) and **7** [20] (0.59 g, 2.12 mmol): **14** (0.09 g, 70%). Yellow liquid. $[\alpha]_D^{25} = +43$ ($c = 1.9$, $CHCl_3$). IR (KBr): 3411, 2945, 2931, 2857, 2010, 1611, 1513, 1463, 1360, 1249, 1087, 837, 778. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.17 (*d*, *J*(*A*,*B*) = 8.3, 2 H); 6.79 (*d*, *J*(*A*′,*B*′) = 8.6, 2 H); 4.38 (*s*, 2 H); 4.34–4.28 (*m*, 2 H); 3.78 (*s*, 3 H); 3.38 (*t*, *J* = 6.7, 2 H); 1.63–1.51 (*m*, 8 H); 1.43–1.25 (*m*, 12 H); 0.93–0.89 (*m*, 12 H); 0.08 (*d*, *J* = 7.1, 6 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 159.3; 130.7; 129.1; 113.7; 86.7; 84.9; 72.4; 62.8; 62.4; 55.0; 38.3; 37.8; 29.6; 29.4; 29.3; 29.2; 26.1; 25.8; 25.1; 22.3; 18.2; 14.1; −4.4; −4.9. ESI-MS: 527 ($[M+Na]^+$).

*(5*R*)-5-{[(*tert*-Butyl)dimethylsilyl]oxy}-16-[(4-methoxybenzyl)oxy]hexadec-6-yn-8-one* (**4**). As described for **3**, from **14** (0.5 g, 0.99 mmol): **4** (0.38 g, 77%). Colorless liquid. $[\alpha]_D^{25} = +41.80$ ($c = 2.2$, $CHCl_3$). IR (KBr): 2930, 2857, 2210, 1714, 1679, 1463, 1254, 1089, 838, 778. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.2 (*d*, *J*(*A*,*B*) = 8.3, 2 H); 6.82 (*d*, *J*(*A*′,*B*′) = 8.3, 2 H); 4.45 (*t*, *J* = 6.4, 1 H); 4.37 (*s*, 2 H); 3.78 (*s*, 3 H); 3.37 (*t*, *J* = 6.4, 2 H); 2.49 (*t*, *J* = 7.1, 2 H); 1.73–1.51 (*m*, 6 H); 1.42–1.25 (*m*, 12 H); 0.94–0.90 (*m*, 12 H); 0.13 (*d*, *J* = 10.0, 6 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 187.0; 159.0; 131.5; 129.1; 113.6; 96.1; 83.1; 72.4; 69.9; 62.7; 55.0; 45.3; 37.6; 29.7; 29.3; 29.2; 27.2; 26.2; 25.7; 23.9; 22.2; 18.2; 14.1; −4.4; −4.9. ESI-MS: 525 ($[M+Na]^+$). HR-MS: 525.3378 ($[M+Na]^+$, $C_{30}H_{50}NaO_4Si^+$; calc. 525.3376).

*(5*R*,8*S*)-5-{[(*tert*-Butyl)dimethylsilyl]oxy}-16-[(4-methoxybenzyl)oxy]hexadec-6-yn-8-ol* (**14a**). As described for **13a**, from **4** (0.30 g, 0.60 mmol): **14a** (0.28 g, 91%). HPLC (*Chiral Pak-IC*, 3% ^{i}PrOH/hexane, flow rate 1 ml/min, 210 nm): t_R (major) 8.488, t_R (minor) 7.978; de 90%. Colorless liquid. $[\alpha]_D^{25} = +25.0$ ($c = 1.85$, $CHCl_3$. IR (KBr): 3409, 2927, 2849, 2191, 1605, 1461, 1349, 1245, 1082, 835, 771. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.17 (*d*, *J*(*A*,*B*) = 8.3, 2 H); 6.80 (*d*, *J*(*A*′,*B*′) = 8.3, 2 H); 4.38 (*s*, 2 H); 4.32 (*t*, *J* = 5.2, 2 H); 3.78 (*s*, 3 H); 3.37 (*t*, *J* = 6.0, 2 H); 1.66–1.52 (*m*, 8 H); 1.43–1.29 (*m*, 12 H); 0.93–0.83 (*m*, 12 H); 0.09 (*d*, *J* = 7.5, 6 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 159.1; 130.7; 129.1; 113.7; 86.6; 85.1; 72.4; 62.8; 62.3; 55.0; 38.4; 37.8; 29.7; 29.5; 29.4; 29.2; 27.2; 25.9; 25.1; 22.3; 18.2; 14.1; −4.5; −5.0. ESI-MS: 527 ($[M+Na]^+$). HR-MS: 527.3555 ($[M+Na]^+$, $C_{30}H_{52}NaO_4Si^+$; calc. 527.3532).

*1,1-{{(1*R*,4*S*)-1-Butyl-4-{[8-[(4-methoxybenzyl)oxy]octyl}but-2-yne-1,4-diyl}bis(oxy)}bis[(*tert*-butyl)dimethylsilane]* (**16**). As described for **15**, from **14a** ((0.25 g, 0.49 mmol): **16** (0.25 g, 81%). Colorless liquid. $[\alpha]_D^{25} = +27.5$ ($c = 1.20$, $CHCl_3$). IR (KBr): 2905, 2829, 2195, 1603, 1505, 1454, 1245, 1075, 820, 767. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.17 (*d*, *J*(*A*,*B*) = 8.3, 2 H); 6.8 (*d*, *J*(*A*′,*B*′) = 8.6, 2 H); 4.38 (*s*, 2 H); 4.31 (*t*, *J* = 6.4, 2 H); 3.78 (*s*, 3 H); 3.38 (*t*, *J* = 6.4, 2 H); 1.62–1.52 (*m*, 8 H); 1.39–1.29 (*m*, 12 H); 0.93–0.89 (*m*, 21 H); 0.08 (*d*, *J* = 7.1, 12 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 159.3; 130.8; 129.3; 113.7; 85.5; 83.8; 72.5; 62.9; 55.2; 38.7; 38.4; 29.8; 29.6; 29.4; 29.2; 26.2; 27.4; 25.8; 25.2; 22.4; 18.2; 14.1; −4.3; −4.9. ESI-MS: 641 ($[M+Na]^+$). HR-MS: 641.4367 ($[M+Na]^+$, $C_{36}H_{66}NaO_4Si_2^+$; calc. 641.4397).

*(9*S*,12*R*)-9,12-Bis{[(*tert*-butyl)dimethylsilyl]oxy}hexadec-10-yn-1-ol* (**18**). As described for **17**, from **16** (0.22 g, 0.36 mmol): **18** (0.12 g, 69%). Colorless liquid. $[\alpha]_D^{25} = +41.8$ ($c = 0.7$, $CHCl_3$). IR (KBr): 3449, 2931, 2857, 2010, 1609, 1572, 1464, 1358, 1252, 1086. ^{1}H-NMR (300 MHz, $CDCl_3$): 4.43 (*t*, *J* = 6.0, 2 H); 3.72 (*t*, *J* = 6.7, 2 H); 1.74–1.61 (*m*, 8 H); 1.51–1.37 (*m*, 12 H); 1.04–1.0 (*m*, 21 H); 0.2 (*m*, 12 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 85.5; 63.0; 38.7; 38.4; 32.8; 29.5; 29.2; 27.4; 25.8; 25.2; 22.4; 18.2; −4.3; −4.9. ESI-MS: 521 ($[M+Na]^+$). HR-MS: 521.3820 ($[M+Na]^+$, $C_{28}H_{58}NaO_3Si_2^+$; calc. 521.3822).

*(9*S*,12*R*)-9,12-Bis{[(*tert*-Butyl)dimethylsilyl]oxy}hexadec-10-ynoic Acid* (**20**). As described for **19**, from **18** (0.10 g, 0.21 mmol): **20** (0.07 g, 86%). Colorless liquid. $[\alpha]_D^{25} = +26.2$ ($c = 1.85$, $CHCl_3$). IR (KBr): 3411, 2931, 2857, 2015, 1678, 1513, 1463, 1249, 1087. ^{1}H-NMR (300 MHz, $CDCl_3$): 4.32 (*t*, *J* = 6.2, 2 H); 2.33 (*t*, *J* = 7.5, 3 H); 1.63–1.61 (*m*, 6 H); 1.40–1.25 (*m*, 12 H); 0.97–0.89 (*m*, 21 H); 0.10 (*d*, *J* = 6.6, 12 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 179.5; 85.6; 62.9; 38.7; 38.4; 33.9; 29.2; 29.1; 27.4; 25.8; 25.1; 24.6; 22.3; 18.2; 14.0; −4.37; −4.96. ESI-MS: 535 ($[M+Na]^+$). HR-MS: 535.3636 ($[M+Na]^+$, $C_{28}H_{56}O_4NaSi_2^+$; calc. 535.3614).

*(9*S*,12*R*)-9,12-Dihydroxyhexadec-10-ynoic Acid* (**2**). As described for **1**, from **20** (0.016 g, 58%): **2** (0.05 g, 0.09 mmol). Colorless liquid. $[\alpha]_D^{25} = -8.3$ ($c = 0.17$, CD_3OD). IR (KBr): 3381, 2928, 2895, 2857, 2020, 1710, 1549, 1459, 1408, 1330, 1075. ^{1}H-NMR (300 MHz, CD_3OD): 4.32 (*t*, *J* = 6.5, 2 H); 2.27 (*t*, *J* = 7.3, 2 H); 1.71–1.55 (*m*, 6 H); 1.50–1.28 (*m*, 12 H); 0.93 (*t*, *J* = 7.1, 3 H). ^{13}C-NMR (75 MHz, CD_3OD):

177.8; 86.4; 62.7; 38.9; 38.7; 35.0; 30.7; 30.3; 30.2; 30.1; 28.5; 26.2; 26.05; 23.4; 14.4. ESI-MS: 307 ($[M+Na]^+$). HR-MS: 307.1896 ($[M+Na]^+$, $C_{16}H_{28}NaO_4^+$; calc. 307.1885).

REFERENCES

[1] D. Faulkner, *J. Nat. Prod. Rep.* **1997**, *14*, 259.
[2] F. Bohlmann, T. Burkhardt, C. Zdero, 'Naturally Occurring Acetylenes', Academic Press, London, 1973, p. 1, 32 and 222.
[3] R. A. Barrow, R. J. Capon, *Aust. J. Chem.* **1994**, *47*, 1901.
[4] S. Nishimura, S. Matsunaga, M. Shibazaki, K. Suzuki, N. Harada, H. Naoki, N. Fusetani, *J. Nat. Prod.* **2002**, *65*, 1353.
[5] M. J. Ortega, E. Zubia, J. L. Caraballo, J. Salva, *J. Nat. Prod.* **1996**, *59*, 1069.
[6] N. Fusteani, H. Y. Li, K. Tamura, S. Matsunga, *Tetrahedron* **1993**, *49*, 1203.
[7] Y. Seo, K. W. Cho, J. R. Rho, J. Shin, *Tetrahedron* **1998**, *54*, 447.
[8] A. D. Patil, W. C. Kokke, S. Cochran, T. A. Francis, T. Tomszek, J. W. Westley, *J. Nat. Prod.* **1992**, *55*, 1170.
[9] Z.-Y. Zhou, F. Wang, J.-G. Tang, L.-Z. Fang, Z.-J. Dong, J.-K. Liu, *J. Nat. Prod*. **2008**, *71*, 223.
[10] P. Radha Krishna, E. Raja Sekhar, V. Kannan, *Tetrahedron Lett.* **2003**, *44*, 4973.
[11] A. V. Rama Rao, P. Radha Krishna, J. S. Yadav, *Tetrahedron Lett.* **1989**, *30*, 1669; M. K. Gurjar, A. M. S. Murugaiah, P. Radha Krishna, C. V. Ramana, M. S. Chorghade, *Tetrahedron: Asymmetry* **2003**, *14*, 1363; G. V. M. Sharma, P. Sreenivas, P. Rajendra Prasad, P. Radha Krishna, M. S. Chorghade, S. V. Ley, *Tetrahedron: Asymmetry* **2005**, *16*, 1113; G. V. M. Sharma, P. Sreenivas, P. Radha Krishna, M. S. Chorghade, S. V. Ley, *Tetrahedron: Asymmetry* **2005**, *16*, 1125.
[12] a) J. S. Yadav, V. Geetha, A. Krishnam Raju, D. Gnaneshwar, S. Chandrasekhar, *Tetrahedron Lett.* **2003**, *44*, 2983; b) J. S. Yadav, P. K. Deshpande, G. V. M. Sharma, *Tetrahedron* **1990**, *46*, 7033; c) L. Xiao, T. Kitazume, *Tetrahedron: Asymmetry* **1997**, *8*, 3597; d) S. Ma, F. Yu, W. Gao, *J. Org. Chem*. **2003**, *68*, 5943.
[13] J. C. Anderson, B. P. Mcdermott, E. J. Griffin, *Tetrahedron* **2000**, *56*, 8747.
[14] S. Vasudeva Naidu, P. Kumar, *Tetrahedron Lett.* **2007**, *48*, 2279.
[15] a) J. Chun, H.-S. Byun, R. Bittman, *J. Org. Chem.* **2003**, *68*, 348; b) S. F. Mayer, A. Steinreiber, R. V. A. Orru, K. Faber, *Eur. J. Org. Chem*. **2001**, *23*, 4537.
[16] K. C. Nicolaou, B. E. Marron, C. A. Veale, S. E. Webber, C. N. Serhan, *J. Org. Chem.* **1989**, *54*, 5527.
[17] S. Chandrasekhar, C. Rambabu, A. Syamprasad Reddy, *Org. Lett*. **2008**, *10*, 4355.
[18] D. E. Frantz, R. Frassler, E. M. Carreira, *J. Am. Chem. Soc.* **2000**, *122*, 1806; D. Boyall, D. E. Frantz, E. M. Carreira, *Org. Lett*. **2002**, *4*, 2605.
[19] a) E. J. Corey, R. K. Bakshi, *J. Am. Chem. Soc.* **1987**, *109*, 5551; b) E. de Lemos, F.-H. Porée, A. Commerçon, J.-F. Betzer, A. Pancrazi, J. Ardission, *Angew. Chem., Int. Ed.* **2007**, *46*, 1917; c) K. A. Parker, M. W. Ledeboer, *J. Org. Chem*. **1996**, *61*, 3214; d) B. M. Trost, J. L. Gunzner, O. Dirat, Y. H. Rhee, *J. Am. Chem. Soc.* **2002**, *124*, 10396; e) S. Pichlmair, M. Lera Ruiz, K. Basu, L. A. Paquette, *Tetrahedron* **2006**, *62*, 5178.
[20] P. Radha Krishna, A. Sreesailam, *Synlett* **2008**, 2795.

Received October 1, 2010