JOC*Article*

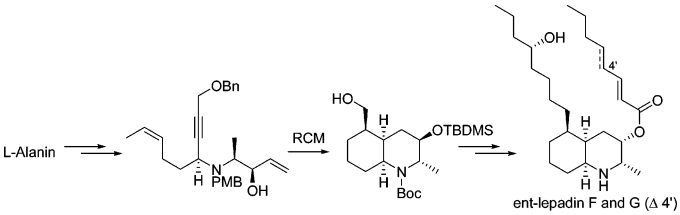
Total Synthesis of ent-Lepadin F and G by a Tandem Ene−Yne−Ene Ring Closing Metathesis

Alexander Niethe, Dirk Fischer, and Siegfried Blechert*

Institut für Chemie, Technische Universität Berlin, Strasse des 17. Juni 135, D-10623 Berlin, Germany

blechert@chem.tu-berlin.de

Received December 20, 2007

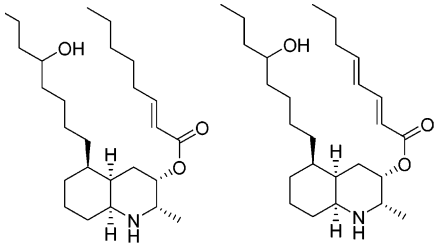


The first total synthesis of the decahydroquinoline-alkaloids lepadin F and G is described. As key steps, the decahydroquinoline skeleton has been synthesized by utilizing a tandem ene−yne−ene ring closing metathesis of an acyclic precursor followed by a stereoselective hydrogenation of the resulting diene moiety. The selectivity of these two steps was achieved by a well-directed hydroxyl protection strategy. The synthesized compounds were found to be enantiomers of natural lepadin F and G, consequently the absolute configuration of the natural compounds could be assigned.

Introduction

Lepadins are members of decahydroquinoline-alkaloids that were found in marine sources. Lepadin A, B, and C where isolated in the early 1990s from the North Sea tunicate *Clavelina lepadiformis*. These compounds have shown remarkable effects against human cancer cells.[1] In 2002 lepadins D−F were discovered by Wright and König[2] from tunicates of the genus *Didemnum*, and Caroll and co-workers[3] have isolated lepadins F−H from *Aplidium tabascum*. Biological studies on lepadins D−F have shown low cytotoxicity but have shown significant and selective activity against malaria causing plasmodia and some trypanosomes, which are the main pathogens of sleeping sickness.[2] Due to the present lack of effectual prophylaxis and curing therapy for these diseases, lepadins are important targets in drug development.

In spite of the pharmacological potential only a few efforts have been made toward the total synthesis of lepadins.[4,5] Presently, no synthesis of lepadin F and G (Figure 1) is described, and prior to our work their absolute configuration has not been determined. Herein we describe the first total synthesis of lepadin F and G.



1 2

FIGURE 1. Proposed structures of lepadin F (**1**) and G (**2**).

As a key step in our synthesis, we planned the construction of the decahydroquinoline-skeleton of the target structures by a tandem ene−yne−ene ring closing metathesis[6] (RCM) of the precursor **5** (Scheme 1) followed by a stereoselective hydro-

(1) (a) Steffan, B. *Tetrahedron* **1991**, *47*, 8729. (b) Kubanek, J.; Williams, D. E.; Silva, E. D. d.; Allen, T.; Anderson, R. J. *Tetrahedron Lett.* **1995**, *36*, 6189−6192.

(2) Wright, A. D.; Goclik, E.; König, G. M.; Kaminsky, R. *J. Med. Chem.* **2002**, *45*, 3067−3072.

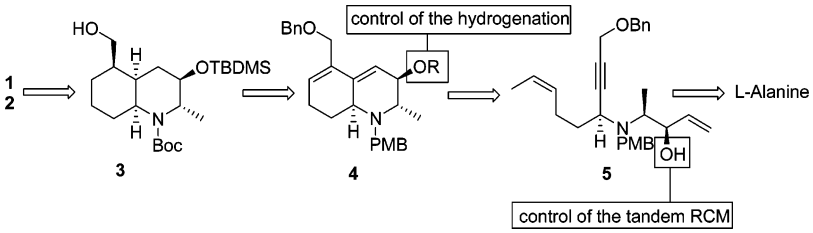
(3) Davis, R. A.; Carroll, A. R.; Quinn, R. J. *J. Nat. Prod.* **2002**, *65*, 454−457.

(4) (a) Toyooka, N.; Okumura, M.; Takahata, H. *J. Org. Chem.* **1999**, *64*, 2182−2183. (b) Ozawa, T.; Aoyagi, S.; Kibayashi, C. *Org. Lett.* **2000**, *2*, 2955−2958. (c) Ozawa, T.; Aoyagi, S.; Kibayashi, C. *J. Org. Chem.* **2001**, *66*, 3338−3347. (d) Kalai, C.; Tate, E.; Zard, S. Z. *Chem. Commun.* **2002**, 1430−1431. (e) Mena, M.; Bonjoch, J. *Tetrahedron* **2005**, 8264−8270; (f) Mena, M.; Valls, N.; Borregan, M.; Bonjoch, J. *Tetrahedron* **2006**, (9166−9173). (g) Barbe, G.; Charette, A. *Abstract of Papers*, *232nd National Meeting of the American Chemical Society*, San Francisco, CA, Sept 10−14, 2006; American Chemical Society: Washington, DC, 2006; ORGN-747. (h) Slafer, B.; et al. *Abstract of Papers*, *227th National Meeting of the American Chemical Society*, Anaheim, CA, March 28-April 1, 2004; American Chemical Society: Washington, DC, 2004; ORGN-396.

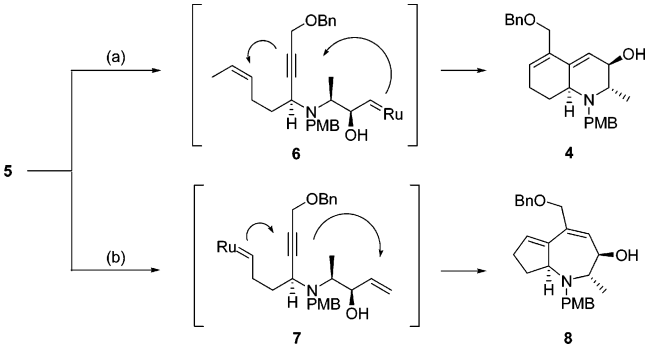
(5) (a) Pu, X.; Ma, D. *Angew. Chem., Int. Ed.* **2004**, *43*, 4222−4225. (b) Pu, X.; Ma, D. *J. Org. Chem.* **2006**, *71*, 6562−6572.

10.1021/jo7027079 CCC: $40.75
Published on Web 03/22/2008

SCHEME 1. Retrosynthesis



SCHEME 2. Tandem RCM of 5, Alternative Reaction Paths



genation of the resulting hexahydroquinoline **4** with concomitant removal of a benzyl and a *p*-methoxybenzyl protecting group. We envisioned that a bulky silyl group on the hydroxyl group of **4** would allow control of stereochemistry in the hydrogenation step.

From **3**, attaching the side chain on the hydroxylmethyl moiety, inversion of the configuration of the ring hydroxyl group, and esterification with either octenoic acid or octadienoic acid would finally lead to lepadin F (**1**) and G (**2**).

For the synthesis of the eight-carbon side chain of lepadin F and G, we projected a concept that allows an enantioselective construction of both enantiomers of the secondary alcohol. Comparison of spectroscopic and chiroptical data of synthesized materials with the data available for natural products would then allow the determination of the actual unknown configuration.

On closer examination of the projected metathesis step, two different reaction pathways could be envisioned (Scheme 2): (a) metathesis may initiate at the terminal double bond to produce Ru−carbene intermediate **6**, which on two consecutive RCMs gives rise to the desired bicycle **4** or (b) metathesis may initiate on the disubstituted alkenyl moiety to produce Ru−carbene species **7**. Tandem RCM would then lead to the[5,7] bicycle **8**. Therefore we intended to leave the allylic hydroxyl group unprotected in the metathesis reactions so that it could exert a coordinative effect in the initial catalyst attack favoring pathway (a) in addition to the preference of attack on monosubstituted alkenes over disubstituted alkenes. Similar effects have been reported earlier by us[7] and others[8] and should be an effective strategy to control the regiochemistry at this step.

(6) For reviews about ene-yne metathesis see: (a) Diver, S. T.; Giessert, A. J. *Chem. Rev.* **2004**, *104*, 1317−1382. (b) Randl, S.; Blechert, S. In *Handbook of Metathesis*; Grubbs, R. H., Ed.; Wiley-VCH: Weinheim, 2003; Vol. 2, pp 151−175. For selected examples see: (c) Fukumoto, H.; Takahashi, K.; Ishihara, J.; Hatakeyama, S. *Angew. Chem., Int. Ed.* **2006**, *45*, 2731−2734. (d) Honda, T.; Namiki, H.; Kaneda, K.; Mizutani, H. *Org. Lett.* **2004**, *6*, 87−89. (e) Zuercher, W. J.; Hashimoto, M.; Grubbs, R. H. *J. Am. Chem. Soc.* **1996**, *118*, 6634−6640.

(7) (a) Michaelis, S.; Blechert, S. *Org. Lett* **2005**, *7*, 5513−5516. (b) Fischer, D. Thesis, Technical University Berlin, Berlin, 2005.

Results and Discussion

For the synthesis of **5** we chose commercially available L-alanine as starting material. Esterification with methanol and reductive amination with 4-anisaldehyde led to the chiral building block **9** (Scheme 3). Following a method described by Knochel et al.[9] further condensation with *cis*-4-hexenal[10] and a copper-catalyzed addition of benzyl propargyl ether to the intermediate iminium species furnished a 1:2 diastereomeric mixture of propargylamines **10** and **11**, which could be separated after reduction with $LiAlH_4$ and column chromatography of the resulting alcohols **12** and **13**.

In initial studies[7b] we were able to perform the three-component-coupling with an increased diastereomeric ratio of 1:8 (**10**:**11**) utilizing R-QUINAP[7b] as the chiral ligand for the copper catalyst. But during the development of the synthetic concept we found that looking beyond the synthesis of lepadin F and G, the synthesis of lepadin B and other lepadins would be accessible from diastereomer **11**. This is why we decided not to perform two single diastereoselective steps toward **10** and **11** but rather to synthesize both substrates in one step with subsequent chromatographic separation. Considering the high costs of chiral ligands, this procedure seemed to us to be the more economical way. Our attempts toward lepadin B and other lepadins continuing from **13** are still in progress and will be reported soon. With isolated **12** in hands we proceeded with the synthesis of lepadin F and G. Therefore alcohol **12** was further converted into aldehyde **14** by Swern oxidation in 99% yield. Addition of vinylmagnesium chloride at −78 °C finally yielded allylic alcohol **5** as a single diastereomer.

When the metathesis precursor **5** was exposed to catalyst **Ru-2**[11] (Scheme 4) in dichloromethane at room temperature or at 40 °C no reaction occurred. For experiments in toluene at 80 °C we chose the very stable catalyst **Ru-3**[12] to avoid catalyst decomposition at higher temperatures. We discovered that although slow heating of a solution of catalyst and substrate did not drive the reaction to completion after 1 day, the addition of dissolved catalyst to a hot solution of the substrate resulted in complete conversion after 3 h. Under these conditions hexahydroquinoline **4** was obtained in 62% yield. We examined other catalysts under identical reaction conditions. Surprisingly,

(8) (a) BouzBouz, S.; Simmons, R.; Cossy, J. *Org. Lett* **2004**, *7*, 3465−3467. (b) Hoye, T. R.; Zhao, H. *Org. Lett.* **1999**, *1*, 1123−1125.

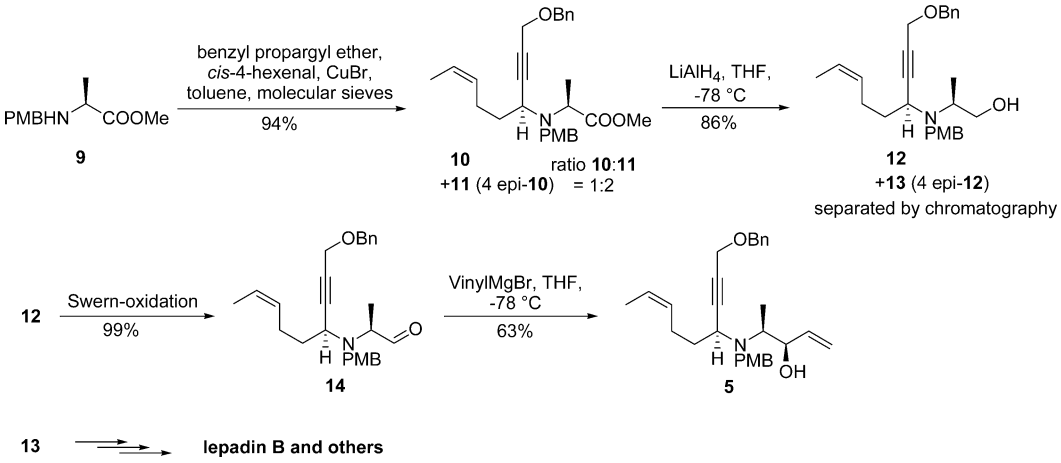
(9) (a) Dube, H.; Gommermann, N.; Knochel, P. *Synthesis* **2004**, *12*, 2015−2025. (b) Gommermann, N.; Koradin, C.; Polborn, K.; Knochel, P. *Angew. Chem., Int. Ed.* **2003**, *42*, 5763−5766.

(10) *cis*-4-Hexenal was synthesized by Swern oxidation from commercially available *cis*-4-hexenol and was used subsequently without further purification.

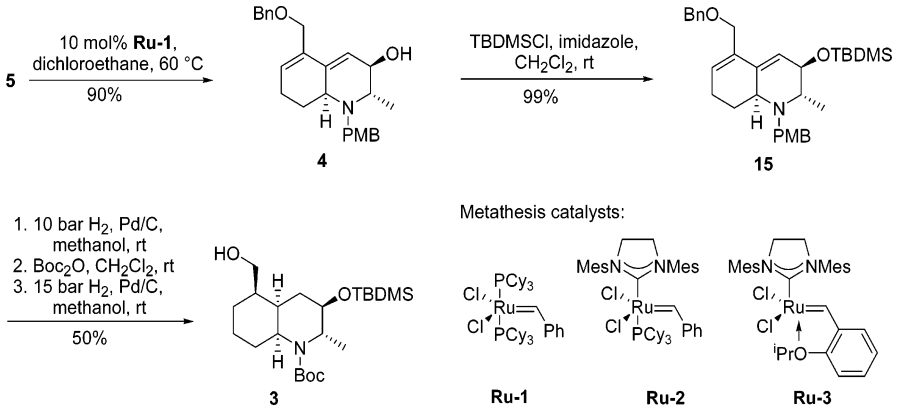
(11) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953.

(12) (a) Garber, S. B.; Kingsbury, J. S.; Gray, B. L.; Hoveyda, H. *J. Am. Chem. Soc.* **2000**, *122*, 8168. (b) Gesslar, S.; Blechert, S. *Tetrahedron Lett.* **2000**, *41*, 9973. (c) Gessler, S.; Randl, S.; Blechert, S. *Tetrahedron Lett.* **2000**, *41*, 9973−9976.

SCHEME 3. Synthesis of Metathesis Precursor 5



SCHEME 4. Transformation of 5 into Decahydroquinoline 3



metathesis with less stable **Ru-1**[13] furnished **4** without significant formation of byproducts as happened during reaction with **Ru-2** and **Ru-3**. At an optimal temperature of 60 °C using **Ru-1** in dichloroethane we were able to achieve an increased yield of 90%. At room temperature the metathesis reaction did not proceed with this catalyst either.

Having established the tandem ene−yne−ene RCM, we next set out to perform the envisioned stereoselective hydrogenation of hexahydroquinoline **4**. Treatment with TBDMSCl and imidazole in dichloromethane generated protected alcohol **15** (Scheme 4), which was directly used in the following step. Hydrogenation with a Pd/C catalyst at 10 bar H_2 pressure resulted in complete reduction of the diene moiety with concomitant cleavage of the PMB-protecting group on the ring nitrogen atom. The benzyl ether, however, was not cleaved in this step. Subsequent reaction with Boc_2O at room temperature followed by a second hydrogenation step with Pd/C yielded decahydroquinoline **3** as colorless crystals in 50% yield over four steps. From a chloroform/heptane solution single-crystals were obtained. The X-ray diffraction analysis confirmed the postulated structure as shown in Figure 2.

Elaboration of the C-5 Side Chain

Recently[14] we described the synthesis of enantiopure hept-1-en-4-ol by a 2-fold copper-catalyzed epoxide ring-opening with Grignard reagents starting from enantiopure epichlorohydrin. Access to both enantiomers of the product as mentioned above is possible either by changing the sequence of Grignard addition or by using the opposite enantiomer of the starting material. We decided to start the synthesis with commercially available (*S*)-epichlorohydrin.

Following this method (*S*)-epichlorohydrin **16** (Scheme 5) was converted into (4*S*)-hept-1-en-4-ol **17** by Grignard addition of ethylmagnesium bromide, subsequent epoxide formation with NaOH, and second Grignard addition of vinylmagnesium bromide. Comparison of the optical rotation of the synthesized

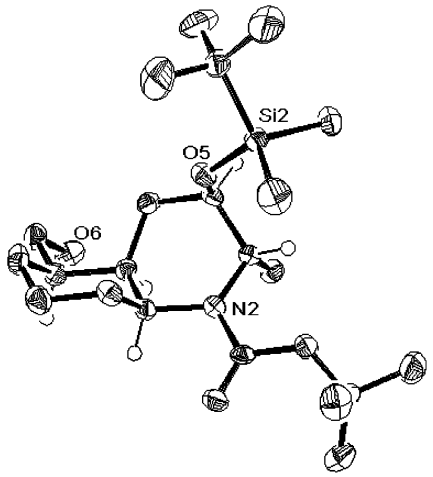
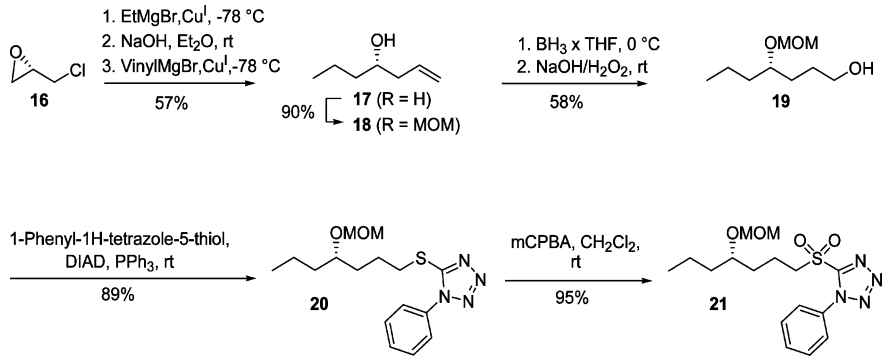


FIGURE 2. ORTEP-structure of **3** as determined by X-ray diffraction.

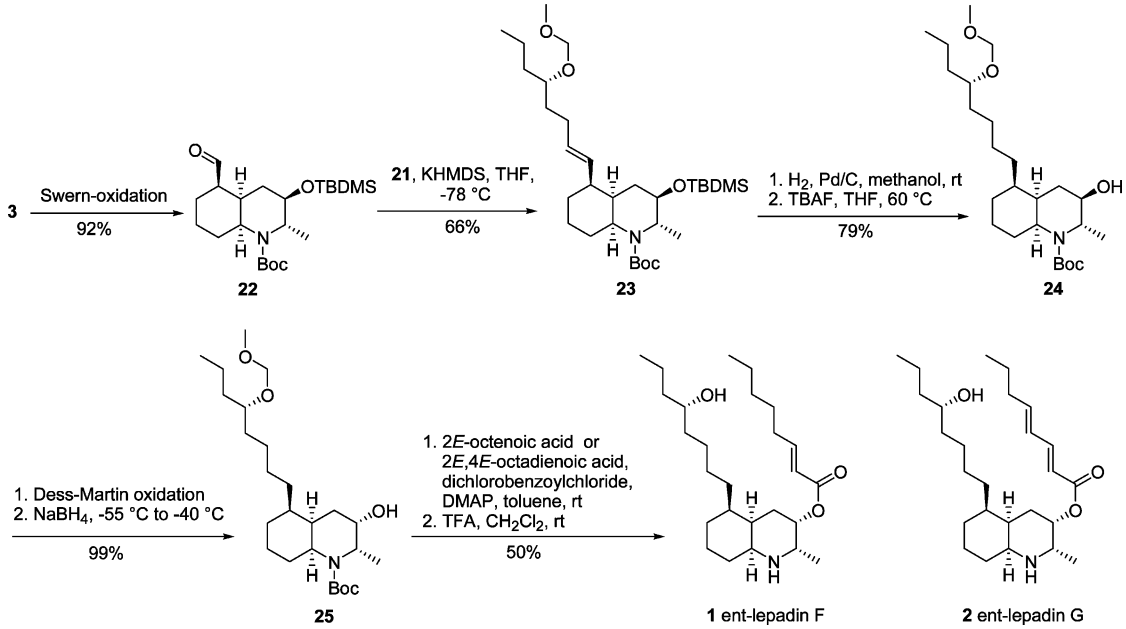
(13) Nguyen, S. T.; Johnson, L. K.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1992**, *114*, 3974.

(14) Holub, N.; Neidhöfer, J.; Blechert, S. *Org. Lett.* **2005**, *7*, 1227−1229.

SCHEME 5. Synthesis of the C-5 Side Chain



SCHEME 6. Synthesis of Lepadin F and G



material with literature data[15] confirmed the retention of configuration. Alcohol **17** was next converted into its MOM-ether **18** by reaction with MOMCl in dichloromethane. Subsequent hydroboration with a large excess of BH_3−THF and oxidative workup led to alcohol **19**. The Mitsunobu reaction with 1-phenyl-1*H*-tetrazole-5-thiole proceeded smoothly to form thioether **20** in 80% yield. Subsequent oxidation with *m*CPBA resulted in sulfonee **21**, which could be used for a side chain attachment by a Julia-Kocienski olefination, as has already been employed in the synthesis of lepadin D, E, and H.[5]

With sulfone **21** in hands we proceeded with the synthesis of lepadin F and G. Swern oxidation of intermediate **3** gave aldehyde **22** (Scheme 6), which was directly used in the Julia-Kocienski olefination with **21**, which proceeded in 66% yield. Hydrogenation of the C−C double bond in **23** and subsequent cleavage of the TBDMS-ether furnished alcohol **24**. Complete inversion of the C-3 carbinol stereocenter was achieved by Dess-Martin oxidation and reduction of the resulting ketone with $NaBH_4$ at −55 °C in methanol. The reaction product **25** was finally used in a Yamaguchi esterification[16] with 2*E*-octenoic acid and 2*E*,4*E*-octadienoic acid[17] to furnish lepadin F **1** and lepadin G **2** each in 50% yield after cleavage of the Boc- and MOM-protecting group with trifluoroacetic acid.

The ^{1}H NMR and ^{13}C NMR spectroscopic data of the synthetic materials were in complete agreement with the literature data. Comparison of the optical rotation identified **2** as the enantiomer of natural lepadin G. **1** could also be determined as an enantiomer of lepadin F after critical comparison with the simultaneously published data by Davis and König: Davis described lepadin F as red oil with positive optical rotation ($\alpha = 5.5°$ in CH_2Cl_2) and König isolated a colorless oil with a negative value ($\alpha = -1.5°$ in $CHCl_3$). Our synthesized material was also colorless with positive values ($\alpha = 1.5°$ in CH_2Cl_2 and 8.8° in $CHCl_3$). It seems likely that the alkaloid should not be a red oil and the different rotation of Davis could be caused by traces of impurities. As a conclusion of these comparisons and the accordance of NMR data, **1** is also the enantiomer of natural lepadin F. Consequently, the absolute configuration of natural lepadin F and G could be assigned as 2*R*,3*R*,4a*S*,5*S*,8a*R*,5′*R*.

In conclusion, we have successfully performed the first total synthesis of lepadin F and G in a longest linear sequence of 19 steps with 2% overall yield. During the linear path only seven chromatographic purifications were necessary. As key steps the decahydroquinoline skeleton was built from an acyclic precursor by a tandem ene−yne−ene ring closing metathesis and a

(15) Riediker, M.; Duthaler, R. O. *Angew. Chem.* **1989**, *101*, 488−490.
(16) Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989.
(17) Coutrot, P.; Snoussi, M.; Savignac, P. *Synthesis* **1978**, 133−134.

stereoselective hydrogenation. The synthesized compounds were identified as enantiomers of the natural products and the absolute configuration of natural lepadin F and G were confirmed. Additional attempts toward the synthesis of other lepadins starting from allylic alcohol **13** are in progress and will be reported soon.

Experimental Section

2*S*-2-[[1-(3-(Benzyloxy)prop-1-ynyl)-hex-4-enyl](4-methoxybenzyl)amino]propionic Acid Methyl Ester (10 and 11). A 21.49 g (219 mmol) sample of *cis*-4-hexenal, 29.09 g (199 mmol) benzyl propargyl ether, and 48.90 g (219 mmol) of **9** were dissolved in 600 mL of toluene. The mixture was treated with 50 g of powdered molecular sieves and 2.87 g (20 mmol) of CuBr and stirred 3 days at room temperature (rt). Afterward the brown-green suspension was filtered over celite and evaporated in vacuo. The residue was redissolved in 400 mL of methyl *tert*-butyl ether and washed with 100 mL of water, 100 mL of 1 N HCl, and 100 mL of saturated aqueous $NaHCO_3$, and the solution was dried over Na_2SO_4 and filtered. A 400 mL aliquot of hexane was added, and the mixture was filtered over a short pad of silica and evaporated in vacuo to give 84.13 g (94%) of a 1:2 diastereomeric mixture of **10** and **11**.

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 1.22−1.23 (d, J = 7.2 Hz, 1H), 1.39−1.40 (d, J = 7.2 Hz, 2H), 1.58−1.74 (m, 5H), 2.02−2.25 (m, 2H), 3.44−3.46 (m, 0.4 H), 3.58−3.61 (m, 0.6 H), 3.64−3.70 (m, 4H), 3.72−3.96 (m, 5H), 4.21 (d, J = 1.6 Hz, 0.7 H), 4.24 (d, J = 1.6 Hz, 1.3 H), 4.61 (s, 0.7 H), 4.62 (s, 1.3 H), 5.26−5.48 (m, 2H), 6.83−6.86 (m, 2H), 7.27−7.32 (m, 3H), 7.34−7.39 (m, 4 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) = 12.8 (CH), 12.9 (CH), 13.4 (CH), 16.7 (CH), 23.8 (CH_2), 23.9 (CH_2), 34.7 (CH_2), 34.9 (CH_2), 49.2 (CH), 50.7 (CH_2), 50.9 (CH_2), 51.1 (CH), 51.2 (CH), 51.6 (CH), 54.7 (CH), 55.3 (CH), 57.1 (CH), 57.5 (CH_2), 57.6 (CH_2), 71.3 (CH_2), 71.4 (CH_2), 80.2 (C), 80.5 (C), 85.6 (C), 86.9 (C), 113.6 (CH), 113.7 (CH), 124.5 (CH), 124.7 (CH), 128.1 (CH), 128.1 (CH), 128.5 (CH), 128.5 (CH), 129.5 (CH), 129.6 (CH), 129.9 (CH), 131.8 (CH), 132.1 (CH), 137.6 (C), 137.6 (C), 158.6 (C), 158.7 (C), 173.6 (C), 174.6 (C). IR (ATR): ν = 3065 (w), 3029 (w), 3009 (w), 2976 (w), 2948 (m), 2938 (m), 2855 (m), 2837 (m), 1734 (s), 1611 (m), 1511 (s), 1454 (m), 1244 (s). MS (EI, 130): m/z (%) = 449, M^+, <1), 116 (52), 390 (30), 380 (40), 121 (100), 91 (22). HR-MS ($C_{28}H_{35}NO_4$): calcd 449.2566, found 449.2567. Anal. Calcd for $C_{28}H_{35}NO_4$: C, 74.80; H, 7.85; N, 3.12. Found: C, 74.64; H, 7.54; N, 2.97.

2*S*,4*S*-2-[[1-(3-(Benzyloxy)prop-1-ynyl)hex-4-enyl](4-methoxybenzyl)amino]propionic Acid Methyl Ester (12) and 2*S*,4*R*-2-[[1-(3-(Benzyloxy)prop-1-ynyl)hex-4-enyl](4-methoxybenzyl)-amino]propionic Acid Methyl Ester (13). A 83.87 g (186 mmol) sample of **10**/**11** was dissolved in 500 mL of THF, and 4.96 g (130 mmol) of $LiAlH_4$ was added portionwise at −78 °C. The solution was slowly warmed to rt overnight, then water was added carefully, and the mixture was filtered over celite. The filtrate was extracted with methyl *tert*-butyl ether, washed with saturated aqueous NaCl, dried over Na_2SO_4 and evaporated in vacuo. After chromatography in hexane/methyl *tert*-butyl ether = 8:2, 20.89 g (27%) of **12** and 45.53 g (59%) of **13** were achieved as colorless oils.

2*S*,4*S*-2-[[1-(3-(Benzyloxy)prop-1-ynyl)hex-4-enyl](4-methoxybenzyl)amino]propionic Acid Methyl Ester (12). RF (hexane/methyl *tert*-butyl ether = 1:1) = 0.29. $[a]^{20}_D$ = +19.9° (c = 1.30, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 1.10−1.12 (d, J = 6.5 Hz, 3H), 1.59−1.61 (m, 4H), 1.67−1.76 (m, 1H), 2.11−2.20 (m, 2H), 2.83 (br s, 1H), 3.14−3.22 (m, 1H), 3.32−3.45 (m, 2H), 3.59−3.63 (m, 1H), 3.73−3.74 (d, J = 4.1 Hz, 2H), 3.80 (s, 3H), 4.25 (s, 2H), 4.63 (s, 2H), 5.28−5.35 (m, 1H), 5.42−5.51 (m, 1H), 6.84−6.86 (d, J = 8.7 Hz, 2H), 7.22−7.25 (m, 2H), 7.28−7.34 (m, 1H), 7.35−7.38 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) = 12.8 (CH_3), 13.8 (CH_3), 24.1 (CH_2), 33.9 (CH_2), 48.1 (CH_2), 53.2 (CH), 55.2 (CH_3), 57.5 (CH_2), 57.9 (CH), 63.9 (CH_2), 71.5 (CH_2), 80.7 (C), 87.2 (C), 113.9 (2 × CH), 124.9 (CH), 127.8 (2 × CH), 128.0 (2 × CH), 128.3 (CH), 128.4 (CH), 129.2 (CH), 129.6 (CH), 132.3 (C), 137.5 (C), 158.6 (C). IR (ATR): ν = 3457 (br m), 3010 (w), 2962 (m), 2934 (m), 2857 (m), 1611 (m), 1511 (s), 1454 (m), 1244 (s), 1072 (s), 1036 (s). MS (EI, 150 °C): m/z (%) = 420 (M^+, <1), 390 (100), 352 (12), 121 (100), 91 (30). HR-MS ($C_{26}H_{32}NO_2$, M − CH_3O): calcd 390.2433, found 390.2433. Anal. Calcd for $C_{27}H_{35}NO_3$: C, 76.92; H, 8.37; N, 3.32. Found: C, 76.54; H, 8.56; N, 3.41.

2*S*,4*R*-2-[[1-(3-(Benzyloxy)prop-1-ynyl)hex-4-enyl](4-methoxybenzyl)amino]propionic Acid Methyl Ester (13). RF (hexane/methyl *tert*-butyl ether = 1:1) = 0.40. $[a]^{20}_D$ = + 128.5° (c = 1.23, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 1.14−1.16 (d, J = 6.6 Hz, 3H), 1.57−1.58 (m, 3H), 1.61−1.67 (m, 1H), 1.75−1.84 (m, 1H), 2.11−2.18 (m, 2H), 2.91 (br s, 1H), 3.08−3.15 (m, 1H), 3.32−3.34 (d, J = 7.9 Hz, 2H), 3.48−3.53 (dddd, J = 1.7, 1.7, 6.2, 8.1 Hz, 1H), 3.57−3.60 (d, J = 13.6 Hz, 1H), 3.77−3.81 (d, J = 13.6 Hz, 1H), 3.80 (s, 3H), 4.26 (s, 2H), 4.64 (s, 2H), 5.25−5.32 (m, 1H), 5.39−5.47 (m, 1H), 6.85−6.87 (d, J = 8.7 Hz, 2H), 7.20−7.26 (m, 2H), 7.28−7.34 (m, 1H), 7.35−7.38 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) = 11.4 (CH_3), 12.8 (CH_3), 23.9 (CH_2), 35.3 (CH_2), 48.4 (CH), 49.9 (CH_2), 54.0 (CH), 55.2 (CH_3), 57.6 (CH_2), 63.1 (CH_2), 71.4 (CH_2), 80.7 (C), 87.2 (C), 113.9 (CH), 124.9 (2 × CH), 127.8 (CH), 128.0 (2 × CH), 128.3 (2 × CH), 128.4 (CH), 129.0 (CH), 130.1 (CH), 131.3 (C), 137.5 (C), 158.6 (C). IR (ATR): ν = 3458 (br m), 3010 (w), 2959 (m), 2934 (m), 2855 (m), 1611 (m), 1512 (s), 1245 (s), 1036 (s). MS (EI, 150 °C): m/z (%) = 421 (M^+, <1), 390 (80), 352 (12), 121 (100), 91 (28). HR-MS ($C_{27}H_{35}NO_3$): calcd 421.2616, found 421.2623. Anal. Calcd for $C_{27}H_{35}NO_3$: C, 76.92; H, 8.37; N, 3.32. Found: C, 76.83; H, 8.23; N, 3.00.

2*S*,3*R*,8a*S*-5-[(Benzyloxy)methyl]-1-(4-methoxybenzyl)-2-methyl-1,2,3,7,8,8a-hexahydroquinolin-3-ol (4). A 6.71 g (15.00 mmol) sample of **5** was dissolved in 500 mL of dichloroethane, the solution was heated to 60 °C, and a solution of 1.23 g (1.50 mmol) of **Ru-1** in 20 mL of dichloroethane was added at this temperature. The mixture was stirred for 3 h at 60 °C, quenched with ethyl vinyl ether, and evaporated in vacuo. Purification by chromatography in hexane/EtOAc = 8:2 gave 5.49 g (90%) **4** as a brown oil.

RF (hexane/EtOAc = 6:4) = 0.30. $[a]^{20}_D$ = −81.43° (c = 1.02, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 0.88−0.91 (d, J = 6.8 Hz, 3H), 1.38−1.46 (m, 1H), 2.25−2.30 (m, 3H), 2.41−2.44 (d, J = 11.0 Hz, 1H), 2.94−2.99 (dq, J = 1.7, 6.7 Hz, 1H), 3.08−3.11 (br d, J = 12.0 Hz, 1H), 3.40−3.43 (d, J = 13.9 Hz, 1H), 3.67−3.71 (m, 1H), 3.79 (s, 3H), 3.99−4.03 (d, J = 13.9 Hz, 1H), 4.08−4.11 (d, J = 11.5 Hz, 1H), 4.16−4.19 (d, J = 11.5 Hz, 1H), 4.51 (s, 2H), 5.89−5.90 (m, 1H), 5.94−5.96 (m, 1H), 6.83−6.87 (m, 2H), 7.23−7.31 (m, 3H), 7.32−7.36 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) = 7.8 (CH_3), 25.2 (CH_2), 27.9 (CH_2), 53.2 (CH_2), 55.2 (CH_3), 55.4, 55.6 (CH), 67.9 (CH), 70.9 (CH_2), 72.1 (CH_2), 113.8 (2× CH), 119.0 (CH), 127.5 (CH), 127.8 (2 × CH), 128.3 (2 × CH), 129.3 (2 × CH), 129.8 (CH, C-6), 131.9 (C), 132.2 (C), 138.0 (C), 138.3 (C), 158.6 (C). IR (ATR): ν = 3422 (br m), 2961 (m), 2930 (m), 2860 (m), 2833 (m), 1611 (m), 1511 (s), 1453 (m), 1244 (s), 1029 (s). MS (EI, 200 °C): m/z (%) = 405 (M^+, <1), 164 (32), 134 (10), 121 (100), 91 (44). HR-MS ($C_{26}H_{31}NO_3$): calcd 405.2303, found 405.2310. Anal. Calcd for $C_{26}H_{31}NO_3$: C, 77.01; H, 7.70; N, 3.45. Found: C, 76.91; H, 7.76; N, 3.47.

2*S*,3*R*,4a*R*,5*R*,8a*S*-3-((*tert*-Butyldimethylsilanyl)oxy)-5-(hydroxymethyl)-2-methyloctahydroquinoline-1-carboxylic Acid *tert*-Butyl Ester (3). A 1.34 g (2.50 mmol) sample of **15** was dissolved in 25 mL of methanol, then 266 mg (0.25mmol) of Pd/C (10%) was added, and the mixture was hydrogenated at 10 bar H_2 pressure for 2 days. The catalyst was filtered off, and the solution was evaporated in vacuo. The residue was treated with 1.09 g (5.00 mmol) of Boc_2O and 2.5 mL of dichloromethane, and the solution was stirred 3 days at rt. Afterward the mixture was dissolved in methyl *tert*-butyl ether, washed with water and saturated aqueous

$NaHCO_3$, dried over Na_2SO_4, and filtered over a short pad of silica. The filtrate was evaporated in vacuo, redissolved in 25 mL of methanol, treated with 266 mg (0.25 mmol) of Pd/C (10%), and stirred under a hydrogen atmosphere (15 bar) for 2 days. After filtration of the catalyst and evaporation of the filtrate in vacuo, chromatography in hexane/EtOAc = 9:1 and 8:2 gave 517 mg (50% over 3 steps) **3** as colorless crystals.

RF (hexane/EtOAc = 6:4) = 0.31; $[a]^{20}_D = +0.65°$ ($c = 0.76$, $CHCl_3$). MP = 122 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 0.04 (s, 3H), 0.05 (s, 3H), 0.86 (s, 9H), 1.05−1.13 (dq, $J = 3.4$, 12.9 Hz, 1H), 1.19−1.21 (d, $J = 6.8$ Hz, 3H), 1.24−1.35 (m, 2H), 1.41−1.52 (m, 2H), 1.45 (s, 9H), 1.70−1.79 (m, 3H), 1.83−1.88 (ddd, $J = 7.3$, 7.3, 14.6 Hz, 1H), 1.97−2.05 (m, 1H), 2.33−2.39 (dddd, $J = 4.4$, 4.4, 4.4, 4.4, 8.0 Hz, 1H), 3.42−3.49 (m, 2H), 3.74−3.80 (m, 2H), 3.80−3.84 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) = −4.8 (CH_3), −4.7 (CH_3), 18.0 (C), 19.5 (CH_3), 22.8, 24.4 (CH_2), 25.7 (3 × CH_3), 26.0, 26.0 (CH_2), 28.5 (3 × CH_3), 31.6 (CH), 42.9 (CH), 53.5, 55.0 (CH), 65.0 (CH_2), 70.4 (CH), 79.0 (C), 155.6 (C). IR (ATR): ν = 3441 (br m), 2953 (s), 2928 (s), 2857 (m), 1688 (s), 1666 (s), 1400 (s), 1365 (s), 1255 (s), 1080 (s). MS (EI, 180 °C): *m*/*z* (%) = 413 (M^+, <1), 300 (100), 282 (24), 256 (16), 182 (10), 91 (22). HR-MS ($C_{22}H_{43}NO_4Si$): calcd 413.2961, found 413.2969. Anal. Calcd for $C_{22}H_{43}NO_4Si$: C, 63.88; H, 10.48; N, 3.39. Found: C, 63.87; H, 10.45; N, 3.40.

2*S*,3*R*,4a*R*,5*R*,8a*S*,5′*S*-3-((*tert*-Butyldimethylsilanyl)oxy)-5-(5-methoxyoct-1-enyl)-2-methyloctahydroquinoline-1-carboxylic Acid *tert*-Butyl Ester (23). A 243 mg (0.66 mmol) sample of **21** was dissolved in 7 mL of THF, and the solution was cooled to −78 °C. Then 1.32 mL (0.66 mmol) of KHMDS (0.5 M in toluene) dissolved in 1 mL of THF was added dropwise, and the resulting solution was stirred for 45 min. Afterward 134 mg (0.33 mmol) of **22** in 3 mL of THF was added dropwise, and the reaction mixture was allowed to warm to rt overnight. Then saturated aqueous NaCl was added, and the mixture was extracted with ethyl acetate, dried over Na_2SO_4, and evaporated in vacuo. Purification by chromatography in hexane/methyl *tert*-butyl ether = 9:1 gave 120 mg (66%) of **23** as a yellow oil.

RF (hexane/EtOAc = 8:2) = 0.33. $[a]^{20}_D = -7.0°$ ($c = 0.80$, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 0.03 (s, 3H), 0.05 (s, 3H), 0.86 (s, 9H), 0.89−0.92 (t, $J = 7.0$ Hz, 3H), 1.18−1.19 (d, $J = 7.4$ Hz, 3H), 1.24−1.41 (m, 7H), 1.44 (s, 9H), 1.49−1.57 (m, 3H), 1.66−1.73 (m, 2H), 1.78−1.85 (ddd, $J = 7.0$, 7.0, 14.3 Hz, 1H), 1.91−2.10 (m, 3H), 2.11−2.23 (m, 2H), 3.38 (s, 3H), 3.50−3.56 (m, 1H), 3.69−3.74 (m, 1H), 3.75−3.79 (m, 1H), 3.79−3.84 (m, 1H), 4.64 (s, 2H), 5.29−5.42 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) = −4.8 (CH_3), −4.7 (CH_3), 14.3 (CH_3), 18.0 (C), 18.5 (CH_2), 19.4 (CH_3), 24.6 (CH_2), 25.3 (CH_2), 25.7 (3 × CH_3), 26.8 (CH_2), 26.9 (CH_2), 28.5 (CH_2), 28.5 (3 × CH_3), 34.3 (CH_2), 35.8 (CH), 36.6 (CH_2), 43.2 (CH), 53.5 (CH), 55.2 (CH), 55.5 (CH_3), 70.7 (CH), 76.8 (CH), 78.9 (C), 95.4 (CH_2), 129.1, 133.3 (CH), 155.6 (C). IR (ATR): ν = 2955 (s), 2929 (s), 2857 (m), 1688 (s), 1394 (m), 1365 (m), 1254 (m), 1042 (s). MS (EI, 230 °C): *m*/*z* (%) = 453 (M^+ − Boc, 16), 408 (100), 396 (60), 378 (72), 364 (44), 334 (44), 290 (20, 260 (16). HR-MS ($C_{26}H_{51}NO_3Si$, M^+ − Boc): calcd 453.3638, found 453.3636.

2*S*,3*S*,4a*R*,5*R*,8a*S*,5′*S*-Oct-2-enoic Acid 5-(5-Hydroxyoctyl)-2-methyldecahydroquinolin-3-yl Ester (1). A 0.013 mL (0.090 mmol) aliquot of 2*E*-octenoic acid, 0.022 mL (0.136 mmol) of iPr_2NEt, and 0.021 mL (0.136 mmol) of trichlorobenzoylchloride were dissolved in 1 mL of toluene, and then a solution of 20 mg (0.045 mmol) of **25** in 1 mL of toluene was added, and the resulting solution was stirred for 45 min at rt. Afterward a solution of 14 mg (0.113 mmol) of DMAP in 1 mL of toluene was added for 45 min, and the resulting solution was stirred an additional 18 h at rt. The mixture was filtered over celite and evaporated in vacuo. The residue was dissolved in 2 mL of dichloromethane, and the solution was treated with 0.2 mL of TFA and stirred 1 h at rt. A 0.05 mL aliquot of 5% aqueous NH_3 was added, and the resulting solution was stirred for 10 min. Then solid Na_2SO_4 was added, and the mixture was filtered and evaporated in vacuo. Purification by chromatograohy in DCM/MeOH/conc NH_3 = 15:1:0.1 gave 9 mg (50%) lepadin F (**1**) as a colorless oil.

RF (DCM/MeOH/conc NH_3 = 15:1:0.1) = 0.13. $[a]^{20}_D = +8.8°$ ($c = 0.25$, $CHCl_3$); $[a]^{20}_D = +1.5°$ ($c = 0.27$, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 0.89 (t, $J = 6.9$ Hz, 3H), 0.92 (t, $J = 7.0$ Hz, 3H), 0.87−0.93 (m, 1H), 1.01−1.03 (d, $J = 6.9$ Hz, 3H), 1.11−1.50 (m, 22H), 1.60−1.71 (m, 3H), 1.73−1.88 (m, 3H), 2.06−2.13 (m, 1H), 2.17−2.23 (m, 2H), 2.88−2.94 (m, 1H), 3.07−3.13 (q, $J = 6.5$ Hz, 1H), 3.53−3.59 (m, 1H), 4.94 (br s, 1H), 5.88−5.92 (dt, $J = 15.6$, 1.6 Hz, 1H), 6.98−7.05 (dt, $J = 15.5$, 7.1 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) = 14.0 (CH), 14.1 (CH), 18.3 (CH), 18.8 (CH_2), 22.4 (CH_2), 23.7 (CH_2), 25.3 (CH_2), 25.7 (CH_2), 26.5 (CH_2), 27.0 (CH_2), 27.7 (CH_2), 29.7 (CH_2), 31.4 (CH_2), 32.2 (CH_2), 32.9 (CH_2), 33.0 (CH_2), 37.5 (CH_2), 39.5 (CH), 39.8 (CH_2), 47.2 (CH), 55.5 (CH), 71.1 (CH), 71.6 (CH), 121.2 (CH), 150.0 (CH) 166.5 (C). IR (ATR): ν = 3313 (br w), 2954 (m), 2927 (s), 2856 (m), 1717 (m), 1653 (m), 1464 (m), 1264 (m), 1172 (m). MS (EI, 170 °C): *m*/*z* (%) = 421 (M^+, 2), 279 (70), 264 (50), 236 (60), 206 (22), 178 (100), 164 (28), 150 (48), 108 (40). HR-MS ($C_{26}H_{47}NO_3$): calcd 421.3555, found 421.3557.

2*S*,3*S*,4a*R*,5*R*,8a*S*,5′*S*-Octa-2,4-dienonic Acid 5-(5-Hydroxyoctyl)-2-methyldecahydroquinolin-3-yl Ester (2). Following the same procedure as described for **1** gave 9 mg (50%) of lepadin G (**2**) as a colorless oil.

RF (DCM/MeOH/conc NH_3 = 15:1:0.1) = 0.21. $[a]^{20}_D = -14.5°$ ($c = 0.27$, CH_2Cl_2). ^{1}H NMR (500 MHz, C_6D_6): δ (ppm) = 0.72 (t, $J = 7.4$ Hz, 3H), 0.77−0.86 (m, 1H), 0.89 (t, $J = 7.0$ Hz, 3H), 1.06−1.07 (d, $J = 6.5$ Hz, 3H), 1.10−1.19 (m, 5H), 1.22−1.36 (m, 12H), 1.38−1.48 (m, 3H), 1.54−1.68 (m, 3H), 1.73.1.85 (m, 3H), 2.12−2.19 (m, 1H), 2.75−2.86 (m, 2H), 3.38−3.43 (m, 1H), 5.02−5.05 (m, 1H), 5.64−5.64−5.72 (dt, $J = 14.3$, 7.0 Hz, 1H), 5.90−5.97 (dd, $J = 15.2$, 11.0 Hz, 1H), 5.95−5.99 (d, $J = 15.2$ Hz, 1H), 7.53−7.59 (dd, $J = 15.2$, 11.0 Hz, 1H). ^{13}C NMR (125 MHz, C_6D_6): δ (ppm) = 14.2 (CH), 15.0 (CH), 19.1 (CH), 19.8 (CH_2), 22.6 (CH_2), 24.6 (CH_2), 26.0 (CH_2), 26.4 (CH_2), 26.6 (CH_2), 27.6 (CH_2), 27.9 (CH_2), 30.7 (CH_2), 33.9 (CH_2), 34.0 (CH_2), 35.6 (CH_2), 38.6 (CH_2), 40.4 (CH), 40.8 (CH_2), 48.1 (CH), 56.3 (CH), 71.7 (CH), 72.0 (CH), 120.8 (CH), 144.6 (CH), 145.8 (CH), 167.1 (C). IR (ATR): ν = 3313 (br w), 2955 (m), 2929 (s), 2857 (m), 1710 (m), 1642 (m), 1464 (m), 1247 (m), 1137 (m), 1000 (m). MS (EI, 170 °C): *m*/*z* (%) = 419 (M^+, <1), 376 (10), 279 (100), 264 (44), 236 (48), 206 (20), 178 (44), 164 (12), 150 (22), 123 (20). HR-MS ($C_{26}H_{45}NO_3$): calcd 419.3399, found 419.3419.

Acknowledgment. We thank Dr. Timm Graening for helpful discussions during the preparation of this manuscript and Dr. Elisabeth Irran for calculation of the X-ray structure.

Supporting Information Available: Experimental procedures for compounds **5**, **9**, **14**−**15**, **17**−**22**, and **24**−**25**, ^{1}H NMR and ^{13}C NMR spectra of all new compounds and the CIF file for compound **3**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO7027079