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The Co-identity of Lipiarmycin A3 and Tiacumicin B

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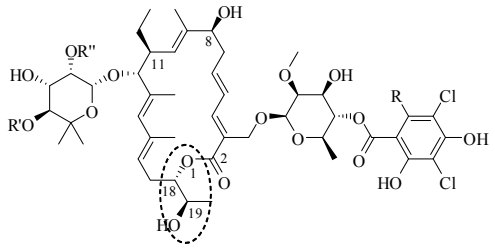
The co-identity of the antibiotics lipiarmycin A3 obtained from *Actinoplanes deccanensis* and tiacumicin B obtained from *Dactylosporangium aurantiacum* was unambiguously demonstrated through a number of experimental means. Spectroscopic analyses performed on both the antibiotics themselves and on their derivatives showed no difference between the two series of compounds. Moreover, unambiguous confirmation of the postulated identity of the two compounds was achieved by chemical degradation of lipiarmycin A3 and isolation of (3*S*,4*R*)-pentane-1,3,4-triol triacetate whose relative configuration was assigned by comparison with the authentic *erythro* and *threo* pentane-1,3,4-triol triacetates, obtained by chemical synthesis.

Keywords: Lipiarmycin A3, Clostomicin B1, Tiacumicin B, *Actinoplanes deccanensis*, *Micromonospora echinospora*, *Dactylosporangium aurantiacum*, Macrolactone antibiotics, Chemical structure revision.

In 1975 Parenti *et al.* [1] reported the isolation from a strain of *Actinoplanes* of an antibiotic substance named lipiarmycin. This material was later recognized to be a mixture of two related products, named lipiarmycin A3 and lipiarmycin A4, characterized by a common 18-membered macro lactone. On the basis of chemical degradations and NMR studies [2], the gross structural formulas (no stereochemistry) of **1** and **2** were assigned to lipiarmycin A3 and lipiarmycin A4, respectively (Figure 1). Further studies [3] revealed that the same strain is also able to produce two minor compounds, lipiarmycin B3 (**3**) and B4 (**4**), respectively which differ from the corresponding A3 and A4 by the position of the isobutyric ester on the rhamnose moiety.



1 R=Et, R'=isobutyryl, R"=H **Lipiarmycin A3**
2 R=Me, R'=isobutyryl, R"=H **Lipiarmycin A4**
3 R=Et, R'=H, R"=isobutyryl **Lipiarmycin B3**
4 R=Me, R'=H, R"=isobutyryl **Lipiarmycin B4**

Figure 1: Chemical structures of lipiarmycins and numbering of the macrocyclic lactone moiety.

Within a few years, several microbial metabolites structurally related to lipiarmycin have been reported, namely clostomicins, from *Micromonospora echinospora* [4], and tiacumicins from *Dactylosporangium aurantiacum* [5]. On the basis of NMR studies, clostomicin B1 and tiacumicin B were recognized to be identical to lipiarmycin A3. The increasing interest in tiacumicin B as a therapeutic agent induced more detailed structural studies on this class of compounds, culminating in the determination of the single crystal X-ray analysis of tiacumicin B. The stereo structure **1**, possessing the (18*S*,19*R*) absolute configuration, was thus assessed for tiacumicin B [6]. In this context, the 19-oxo analogue of tiacumicin B was obtained and reduced with $NaBH_4$ in methanol. This process was expected to afford the (19*S*)-configurated diastereoisomer of **1**. As a consequence, the spectroscopic analyses of the latter compound were not compared to those of tiacumicin B but appeared to be identical to those reported for lipiarmycin A4. However, the NMR spectra of the semi-synthetic material and of the tiacumicin B (of unambiguously determined configuration) were acquired in different solvents, thus inhibiting the evaluation of the subtle spectroscopic differences between the two. Following the same reasoning, to lipiarmycin A4 was assigned the (19*S*) configuration [6] without any further confirmatory X-ray analysis.

The above results, as highlighted in a recent review article on the chemistry of tiacumicin [7], open the question of the identity of lipiarmycin A3 and tiacumicin B. In fact, in our hands, samples of tiacumicin B from *Dactylosporangium auranticum* and lipiarmycin A3 from *Actinoplanes* show absolutely superimposable proton and carbon spectra both in methanol and in chloroform, which strongly suggests that they have the same structure. To substantiate this conclusion we report here on degradation experiments performed on lipiarmycin A3 produced from *Actinoplanes* [1] which unequivocally support this view.

In the first instance, a commercial sample of tiacumicin B from *Dactylosporangium auranticum* [5] was transformed, as earlier described [2], into compound **5** (Figure 2). The NMR data of **5** (see Table S1 and the spectra reported in the supplementary data) were compared with those of the analogous compound from *Actinoplanes*, taking particular care with the signals relative to the positions under discussion, *i.e.* 18 and 19. As expected, within the limits of the technique, the compared materials were identical. In particular, in compound **5** the fragment C_{17}–C_{18}–C_{19} shows very small values for the vicinal coupling constants $J(H_{17b},H_{18})$ and $J(H_{18},H_{19})$ (less than 1 Hz), indicating that this fragment adopts a rigid conformation. Reasonably a difference in the stereochemistry of C_{19} should induce some variations of the chemical shifts and coupling constant of the neighboring protons, which were not observed.

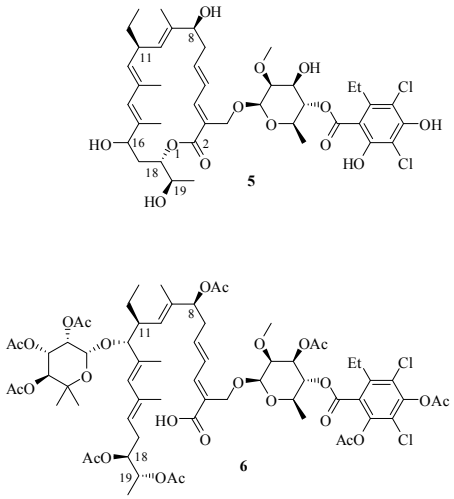


Figure 2: The lactone **5** and the peracetate derivative **6** obtained by degradation of tiacumicin B and lipiarmycin A3, respectively.

Accordingly, with the intent to obtain a clear-cut demonstration of the relative stereochemistry at positions 18 and 19 of the materials of different microbial origin, we studied a chemical degradation leading to a stable and smaller derivative containing the diol framework under investigation. More specifically, we selected the peracetate **6** as a suitable starting material since it can afford either 1,3,4-pentane triol derivatives **7** or **8** (Figure 3) through oxidative cleavage of the C(15)-C(16) double bond, followed by reduction of the obtained aldehyde.

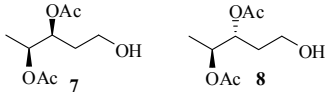


Figure 3: The *threo* and *erythro* diacetates **7** and **8**, respectively obtained by degradation of the peracetate **6**.

The relative stereochemistry of the aforementioned derivative can be determined definitely provided that its analytical data were compared with those obtained from authentic samples of both isomers **7** and **8**. Consequently, we devised two stereoselective and straightforward syntheses of these compounds (Figure 4). The first one starts with the reduction of commercial (*E*)-methyl-3-pentenoate **9** with $LiAlH_4$ followed by protection of the resulting pentenol as the TBDPS ether. The obtained compound **10** was treated with catalytic potassium osmate and *N*-methylmorpholine-*N*-oxide. The stereospecific *syn* dihydroxylation of the (*E*)-double bond afforded the corresponding *threo* diol, which was not isolated, but acetylated to give compound **11**. TBAF in dry THF cleaved efficiently the silyl ether functional group to give the 1,3,4-pentantriol diacetate **7** contaminated with an isomeric diacetyl derivative, most likely formed by 1-3 acetyl scrambling. Hence, we decided to switch our synthetic target to the triacetate derivative, which is obtainable in a single isomeric form. Accordingly, we treated the reaction mixture with Ac_2O/Py to afford pure **12**. Concerning the preparation of the *erythro* triacetate **16**, we selected 3-pentyne-1-ol (**13**) as the starting material for its synthesis. The protection of the hydroxyl functional group as TBDPS ether gave compound **14**, which was hydrogenated in the presence of Lindlar catalyst to afford the corresponding (*Z*)-double bond derivative. The subsequent treatment with catalytic potassium osmate and *N*-methylmorpholine-*N*-oxide provided the stereospecific *syn* dihydroxylation of the (*Z*)-double bond affording the corresponding *erythro* diol, which was acetylated to give compound **15**. As described above, the silyl ether functional group was cleaved using

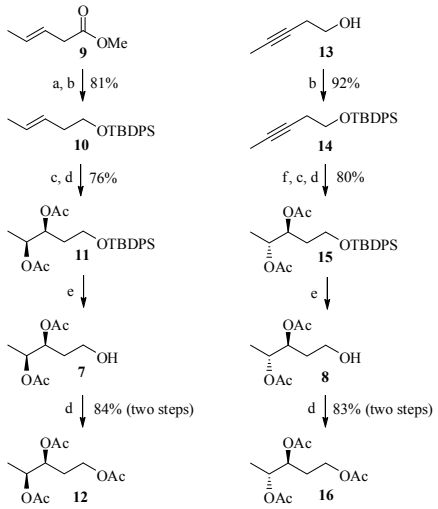


Figure 4: The stereoselective synthesis of the *threo* and *erythro* triacetate **12** and **16**, respectively. Reagents and conditions: a) $LiAlH_4$, Et_2O; b) TBDPSCl, imidazole, DMAP cat., DMF, rt 3 h; c) NMO, $K_2OsO_4.2H_2O$, acetone/H_2O, rt, 24 h; d) Ac_2O, Py, DMAP; e) TBAF, THF, rt, 4 h; f) H_2, AcOEt, Lindlar catalyst.

TBAF in THF and the obtained diacetyl derivative **8** was acetylated to give triacetate **16** in a single diastereoisomeric form.

With the above reference materials in hand, the peracetylated derivative (–)-**6** was ozonized and then reduced with $NaBH_4$ (Figure 5). The obtained diacetate **8** was treated with acetic anhydride in pyridine to afford the desired ester **16**. The triacetate of 1,3,4-pentane triol, {$[\alpha]_D$ –17.1 (c = 2.3, $CHCl_3$)}, eventually obtained from peracetylated acid (–)-**6** derived from **1** from *Actinoplanes*, was compared with synthetic **12** and **16**. Apart from the rotation they were identical to the product with *anti* stereochemistry. In addition, we accomplished a further confirmatory experiment by means of GC analysis. Actually, we recorded different retention times when triacetate **12** and **16** were analysed using the same GC condition.

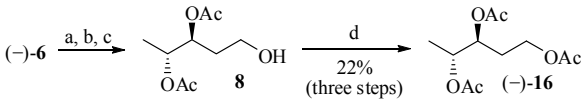


Figure 5: The stereoselective synthesis of the triacetate (–)-**16** by degradation of peracetate (–)-**6** obtained from lipiarmycin A3. Reagents and conditions: a) O_3, MeOH/CH_2Cl_2, –78°C; b) $NaBH_4$, from –78°C to rt; c); chromatographic separation of **8**; d) Ac_2O, Py, DMAP.

We thus prepared two samples containing a 1:1 mixture of the above described triacetate from lipiarmycin and either triacetate **12** or **16**. As a result, we recorded two sharp peaks for the analysis of the former sample and a single sharp peak for the analysis of the latter. All these results, seen together, allows the unambiguous assignment to lipiarmycin A3 from *Actinoplanes* the (18*S*,19*R)* configuration and, consequently, the same structure as that reported for tiacumicin B from *Dactylosporangium*.

Experimental

General: All moisture-sensitive reactions were carried out under a static atmosphere of nitrogen. All reagents were of commercial quality. TLC: Merck silica gel 60 F_{254} plates. CC: silica gel. GC-MS analyses: HP-6890 gas chromatograph equipped with a 5973 mass detector, using a HP-5MS column (30 m × 0.25 mm, 0.25 μm film thickness; Hewlett Packard) with the following temp. program: 60° (1 min) – 6°/min – 150° (1 min)– 12°/min – 280° (5 min); carrier gas, He; constant flow 1 mL/min; split ratio, 1/30; t_R given in min:

t_R(**12**) 17.51, t_R(**16**) 17.09; mass spectra: *m/z* (rel.%). Mass spectrum of compounds **5** and **6** were recorded on a Bruker ESQUIRE 3000 PLUS spectrometer (ESI detector). Optical rotations: Jasco-DIP-181 digital polarimeter, measured at 20°C. Melting points were measured on a Reichert apparatus, equipped with a Reichert microscope, and are uncorrected. ^{1}H and ^{13}C spectra and DEPT experiments: $CDCl_3$ solns. at rt; Bruker-AC-400 spectrometer at 400, 100 and 100 MHz, respectively; chemical shifts in ppm relative to internal $SiMe_4$ (=0 ppm), *J* values in Hz. The analysis of the NMR spectra of compound **5** was carried out at 500 MHz on the Bruker AV 500 spectrometer. The assignment of the proton and carbon nuclei in the spectra were performed through homonuclear COSY and heteronuclear HSQC and HMBC bidimensional experiments.

Lipiarmycin A3 (−)-**1**: from *Actinoplanes deccanensis*, ATCC 21983, was supplied by Olon S.p.A.

Tiacumicin B (−)-1: from *Dactylosporangium auranticum*, subsp. *Hamdenensis,* NRRL 18085, was supplied by Olon S.p.A.

Lactone (−)-5 and peracetate (−)-6: These were prepared by degradation of tiacumicin B from *Dactylosporangium auranticum* and lipiarmycin from *Actinolanes deccanensis* respectively, according to the procedure previously described [2]. Their physical data (melting points, optical rotation values) are in good agreement with those previously reported.

The NMR data of compound (−)-**5** are reported in the supplementary data section.

The chemical structures of (−)-**5** and (−)-**6** were further confirmed by mass analysis:
(−)-**5**: MS (ESI): 849.6 [M+Na$^+$], 825.5 [M–H$^+$]
(−)-**6**: MS (ESI): 1405.8 [M+Na$^+$], 1381.9 [M–H$^+$]

(2*SR*,3*SR*)-5-(*tert*-Butyldiphenylsilyloxy)pentane-2,3-diol diacetate (11): A solution of (*E*)-methyl-3-pentenoate (**9**) (2.3 g, 20.2 mmol) in dry diethyl ether (10 mL) was added dropwise to a stirred mixture of $LiAlH_4$ (0.76 g, 20 mmol) in dry diethyl ether (40 mL). The reaction was heated at reflux for 1 h then was cooled (0°C) and diluted with diethyl ether (80 mL). The resulting mixture was vigorously stirred whilst a solution of NaOH (30% wt. in water, 20 mL) was carefully added. The resulting clear organic phase was separated from the insoluble aluminate salts stuck to the flask surface, which were further rinsed with diethyl ether (2 x 30 mL). The combined organic phase was washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. The residue was dissolved in dry DMF (20 mL) and treated with imidazole (1.5 g, 22 mmol), DMAP (0.1 g, 0.8 mmol) and *tert*-butylchlorodiphenyl silane (6 g, 21.8 mmol) stirring at rt for 3 h. The reaction was then quenched by the addition of a saturated solution of $NaHCO_3$ (100 mL) and was extracted with diethyl ether (2 x 100 mL). The combined organic phase was dried (Na_2SO_4) and concentrated under reduced pressure. The residue was chromatographed using *n*-hexane/diethyl ether (95:5–9:1) as eluent to afford pure **10** (5.3 g, 81% yield) .
Colorless oil
^{1}H NMR (400 MHz, $CDCl_3$): 1.05 (9H, s), 1.63 (3H, dm, *J* = 5.5 Hz), 2.24 (2H, br q, *J* = 6.7 Hz), 3.67 (2H, t, *J* = 6.7 Hz), 5.35-5.51 (2H, m), 7.32-7.44 (6H, m), 7.64-7.71 (4H, m).
^{13}C NMR (100 MHz, $CDCl_3$): 17.9 (Me), 19.2 (C), 26.9 (Me), 36.0 (CH_2), 64.1 (CH_2), 126.9 (CH), 127.6 (CH), 127.7 (CH), 129.5 (CH), 134.2 (C), 135.6 (CH).

A sample of compound **10** (5.1 g, 15.7 mmol) was dissolved in acetone/water (85:15, 60 mL) and the solution was treated with NMO (50% wt. in H_2O, 6 g, 25.6 mmol) and catalytic $K_2OsO_4.2H_2O$ (37 mg, 0.1 mmol) stirring under nitrogen at rt until the starting olefin was not longer detectable by TLC analysis (24 h). The reaction was then quenched by addition of an aqueous solution of sodium hydrosulfite (5% wt., 100 mL) and the acetone was evaporated under vacuum. The pH of the resulting aqueous solution was adjusted to pH 5 by careful addition of diluted HCl aq. and the mixture was extracted with EtOAc (3 x 100 mL). The combined organic phases were dried (Na_2SO_4) and concentrated *in vacuo*. The residue was dissolved in pyridine (25 mL) and treated with acetic anhydride (25 mL) and catalytic DMAP (0.1 g, 0.8 mmol) at rt for 6 h. The volatiles were removed using a rotary evaporator and the residue was purified by chromatography using *n*-hexane/EtOAc (9:1–7:3) as eluent to afford pure **11** (5.3 g, 76% yield).
Colorless oil
^{1}H NMR (400 MHz, $CDCl_3$): 1.05 (9H, s), 1.18 (3H, d, *J* = 6.5 Hz), 1.72-1.88 (2H, m), 2.00 (3H, s), 2.02 (3H, s), 3.60-3.72 (2H, m), 5.02 (1H, dq, *J* = 6.5, 4.8 Hz), 5.18 (1H, dt, *J* = 8.3, 4.8 Hz), 7.33-7.45 (6H, m), 7.61-7.68 (4H, m).
^{13}C NMR (100 MHz, $CDCl_3$): 16.2 (Me), 19.1 (C), 20.8 (Me), 21.0 (Me), 26.8 (Me), 33.4 (CH_2), 59.8 (CH_2), 70.7 (CH), 71.9 (CH), 127.7 (CH), 129.6 (CH), 133.6 (C), 133.6 (C), 135.6 (CH), 135.6 (CH), 170.1 (C), 170.2 (C).

(2*RS*,3*SR*)-5-(*tert*-Butyldiphenylsilyloxy)pentane-2,3-diol diacetate (15): A solution of 3-pentyn-1-ol (**13**) (2 g, 23.8 mmol), imidazole (1.7 g, 25 mmol) and DMAP (0.1 g, 0.8 mmol) in dry DMF (20 mL) was treated with *tert*-butylchlorodiphenyl silane (6.8 g, 24.7 mmol) stirring at rt for 3 h. The reaction was then quenched by the addition of a saturated solution of $NaHCO_3$ (100 mL) and extracted with diethyl ether (2 x 100 mL). The combined organic phases were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was chromatographed using *n*-hexane/diethyl ether (95:5–9:1) as eluent to afford pure **14** (7.1 g, 92% yield).
Colorless oil
^{1}H NMR (400 MHz, $CDCl_3$): 1.05 (9H, s), 1.74 (3H, t, *J* = 2.6 Hz), 2.36-2.43 (2H, m), 3.74 (2H, t, *J* = 7.2 Hz), 7.33-7.45 (6H, m), 7.65-7.71 (4H, m).
^{13}C NMR (100 MHz, $CDCl_3$): 3.4 (Me), 19.2 (C), 22.9 (CH_2), 26.8 (Me), 63.0 (CH_2), 76.1 (C), 76.7 (C), 127.6 (CH), 129.6 (CH), 133.8 (C), 135.6 (CH).

A sample of compound **14** (4.1 g, 12.7 mmol) in EtOAc (50 mL) was hydrogenated at rt and atmospheric pressure in the presence of Lindlar catalyst (5% palladium content, 200 mg). After absorption of 1.05 eq. of hydrogen, the catalyst was removed by filtration and the solvent was evaporated under reduced pressure. The residue was dissolved in acetone/water (85:15, 50 mL) and the solution was dihydroxylated and acetylated as described above for the transformation of compound **10** into diacetate **11**, to give pure **15** (4.5 g, 80%).
Colorless oil
^{1}H NMR (400 MHz, $CDCl_3$): 1.05 (9H, s), 1.19 (3H, d, *J* = 6.6 Hz), 1.70-1.90 (2H, m), 1.97 (3H, s), 2.01 (3H, s), 3.60-3.74 (2H, m), 5.10 (1H, dq, *J* = 6.6, 3.4 Hz), 5.17 (1H, dt, *J* = 9.2, 3.4 Hz), 7.33-7.46 (6H, m), 7.61-7.70 (4H, m).
^{13}C NMR (100 MHz, $CDCl_3$): 15.0 (Me), 19.1 (C), 20.9 (Me), 21.0 (Me), 26.8 (Me), 32.3 (CH_2), 59.9 (CH_2), 70.8 (CH), 71.8 (CH), 127.6 (CH), 129.6 (CH), 133.5 (C), 133.7 (C), 135.5 (CH), 135.6 (CH), 170.2 (C), 170.3 (C).

(3*SR*,4*SR*)-Pentane-1,3,4-triol triacetate (12): A sample of the diacetate **11** (3.2 g, 7.2 mmol) in dry THF (5 mL) was treated at rt

with TBAF (10 mL of a 1 M solution in THF). When the silyl ether was completely cleaved (4 h), the solvent was removed from the reaction mixture using a rotary evaporator and the residue was dissolved in pyridine (20 mL) and treated at rt with acetic anhydride (20 mL) and catalytic DMAP (0.1 g, 0.8 mmol). When the starting alcohol was no longer detectable by TLC analysis (3 h) the volatiles were remove under reduced pressure and the residue was chromatographed using *n*-hexane/EtOAc (95:5–8:2) as eluent to afford pure **12** (1.5 g, 84% yield) .
Colorless oil
^{1}H NMR (400 MHz, $CDCl_3$): 1.21 (3H, d, J = 6.5 Hz), 1.82-1.99 (2H, m), 2.04 (3H, s), 2.06 (3H, s), 2.09 (3H, s), 4.09 (2H, dd, J = 7.0, 5.9 Hz), 4.99-5.12 (2H, m).
^{13}C NMR (100 MHz, $CDCl_3$): 16.0 (Me), 20.7 (Me), 20.7 (Me), 20.9 (Me), 29.6 (CH_2), 60.4 (CH_2), 70.4 (CH), 71.5 (CH), 170.1 (C), 170.2 (C), 170.8 (C).
GC-MS (EI): *m/z* (%) = 186 [M^+–AcOH] (1), 159 (96), 145 (7), 126 (11), 117 (100), 99 (68), 84 (55), 72 (11), 57 (31).

(3*SR*,4*RS*)-Pentane-1,3,4-triol triacetate (16): According to the above reported procedure, a sample of the diacetate **15** (4.1 g, 9.3 mmol) was transformed into triacetate **16** (1.9 g, 83% yield).
Colorless oil
^{1}H NMR (400 MHz, $CDCl_3$): 1.22 (3H, d, J = 6.5 Hz), 1.83-2.00 (2H, m), 2.05 (3H, s), 2.05 (3H, s), 2.07 (3H, s), 4.02-4.17 (2H, m), 4.99-5.13 (2H, m).
^{13}C NMR (100 MHz, $CDCl_3$): 15.0 (Me), 20.8 (Me), 20.9 (Me), 21.0 (Me), 28.4 (CH_2), 60.4 (CH_2), 70.4 (CH), 71.2 (CH), 170.2 (C), 170.3 (C), 170.9 (C).
GC-MS (EI): *m/z* (%) = 186 [M^+–AcOH] (1), 159 (98), 145 (7), 126 (10), 117 (100), 99 (71), 84 (56), 72 (11), 57 (34).

(3*S*,4*R*)-Pentane-1,3,4-triol triacetate (−)-16: A stream of oxygen containing ozone was bubbled through a solution of the acid (−)-**6** (1.9 g, 1.37 mmol) in MeOH/CH_2Cl_2 (1:1 v/v, 120 mL) at −78°C. As soon as the color of the solution turned from pale yellow to permanent light blue, the generation of the ozone was interrupted and the oxygen stream was switched to a nitrogen stream. After a few minutes the solution became yellow and $NaBH_4$ (1.1 g, 29.1 mmol) was added portionwise. The reaction was then warmed to rt, diluted with water (100 mL) and extracted with CH_2Cl_2 (5 x 50 mL). The organic phase was washed with brine, dried (Na_2SO_4) and concentrated *in vacuo*. In order to isolate any possible isomers of compounds of type **7** or **8**, the residue was roughly chromatographed using *n*-hexane/EtOAc (8:2–1:2) as eluent. The fractions containing compounds with an Rf similar to that of either **7** or **8** (by TLC analysis) were collected and concentrated. The residue was dissolved in pyridine (10 mL) and treated at rt with acetic anhydride (10 mL) and catalytic DMAP (0.1 g, 0.8 mmol). After 3 h the volatiles were removed under reduced pressure and the residue was chromatographed using *n*-hexane/EtOAc (95:5–8:2) as eluent to afford pure **16** (75 mg, 22% yield) .
Colorless oil
$[\alpha]_D$: −17.1 (*c* 2.3, $CHCl_3$).
^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (100 MHz, $CDCl_3$) were superimposable on those recorded for **16** and in good agreement with those reported in the Lit. [8].

Supplementary data: Copies of the ^{1}H NMR and ^{13}C NMR spectra of compounds **5**, **12** and **16**, as well as the GC analyses are available.

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