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CHEMISTRY OF PLEUROMUTILINS - 12.

A CYCLOPROPYL CONJUGATED SYSTEM WITHIN THE TRICYCLIC SKELETON OF THE DITERPENE PLEUROMUTILIN: FORMATION AND SYNTHETIC USE

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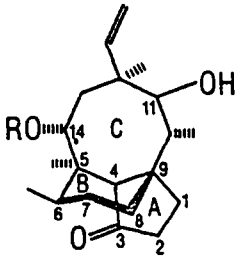
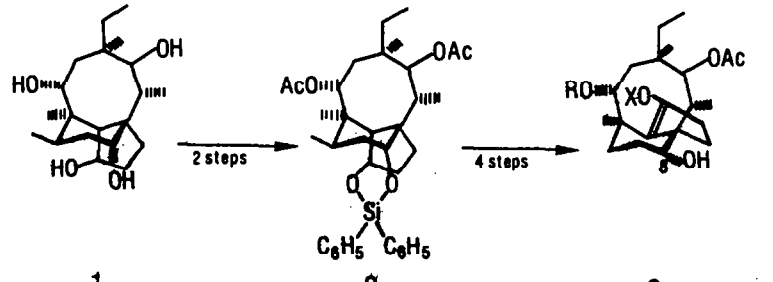
Abstract: The conversion of γ-substituted enol ethers to conjugated cyclopropyl ketones which are part of the skeleton of pleuromutilin is described. The nucleophilic opening of the cyclopropane ring is shown to proceed in a highly stereospecific manner. The cyclopropane bond which is cleaved (C_8-C_4) is the one exhibiting the maximum overlap with the π-orbital of the carbonyl group. This reaction offers a convenient method for the stereospecific introduction of an equatorial fluorine at C_8.

The cytochrome-dependent metabolism of antibacterial active pleuromutilin derivatives leads mainly to products which are hydroxylated in the 2β- or 8α-position, respectively[1]. These products are almost devoid of biological activity. Enhanced stability against metabolic degradation could be gained by introduction of deuterium or fluorine at these positions[2]. In this paper we are reporting on the introduction of fluorine at the 8β-position by stereospecific ring opening of a cyclopropane intermediate.



R = $COCH_2OH$ pleuromutilin
R = H mutilin

Starting from the 8α-hydroxymutilin 1 which is readily available from fermentation sources[3] the silyl-protected enol ethers 3,4 were obtained in a six-step synthesis (1 → 2 → 3,4)[4]



1

2

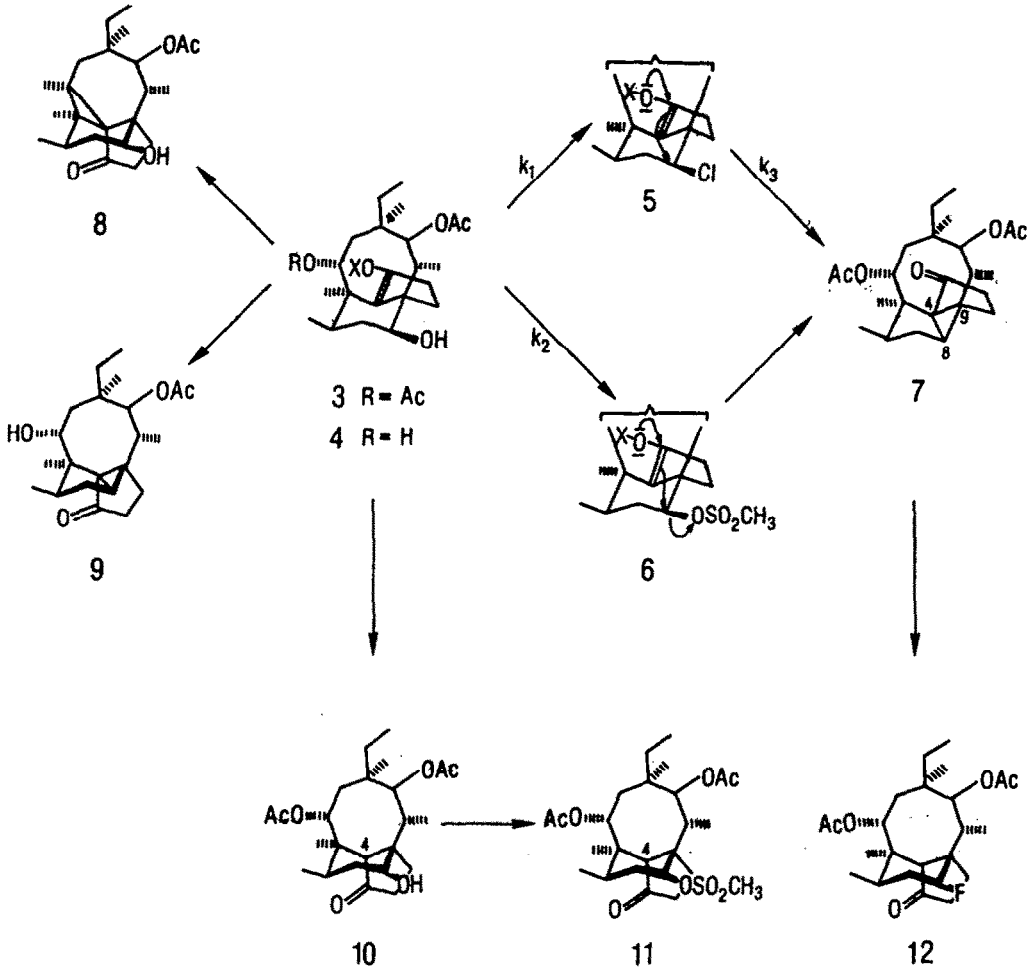
3 R = $COCH_3$

4 R = H

Ac = $COCH_3$

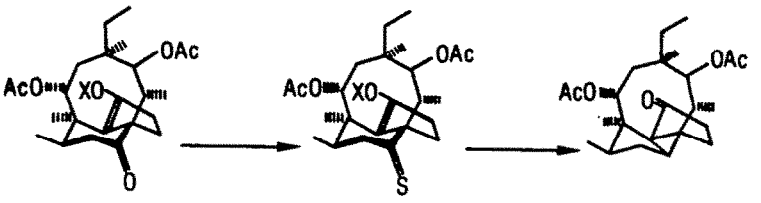
X = $Si(CH_3)_2(t\text{-}C_4H_9)$

Since it is well known that methylsulfonate ester of γ-ketoalcohols are converted on basic treatment to cyclopropane derivatives[5,6], we first tried to esterify the 8β-OH-group of 3 with CH_3SO_2Cl in dry pyridine. This reaction afforded directly the cyclopropylketone 7 without any trifling amount of the expected intermediate 6. From a study of models this result appeared reasonable since the position of the π-orbital of 3 is extremely favourable for an immediately following displacement reaction. If, however the reaction is carried out with the 8,14-dihydroxy compound 4 under equal conditions the cyclopropylketones 8 and 9 are obtained depending on which sulfonate is formed primarily. According to these results evidence is given that both centres of the tricyclic skeleton C_8 and C_{14} are equally well accessible by the π-orbital at C_4. On the contrary there is obviously no cyclization found on reacting the AB-cis fused γ-keto alcohol 10 under the above mentioned conditions. The required electrons for the displacement reaction at C_8 are not available in this case, since they are positioned at the very opposite side at C_4.



The cyclopropylketone 7 gave upon reaction with Olah's HF-pyridine complex the 8-β-fluorocompound as a single product in reasonable yield. The high specificity of this reaction can be rationalized by considering the cyclopropyl bond overlap with the π-system of the carbonyl group. Usually the course of such reactions is controlled by that bond of the cyclopropane moiety which better overlaps the π-system of the adjacent unsaturated centre[7,8]. Owing to the geometry of our strained system, the C_4-C_9 bond does not overlap to any great extent with the π-system, whereas the C_4-C_8 bond is that placed to permit excellent overlap.

In this context it is worth mentioning that the 8-thioxo group exhibits some kind of leaving group properties. The reaction of the 8-thioxoenol ether with Raney-nickel afforded an elimination product which was proved to be identical with the cyclopropylketone 7.



13 14 7

Ac = $COCH_3$

X = $Si(CH_3)_2(t\text{-}C_4H_9)$

Kinetic measurements

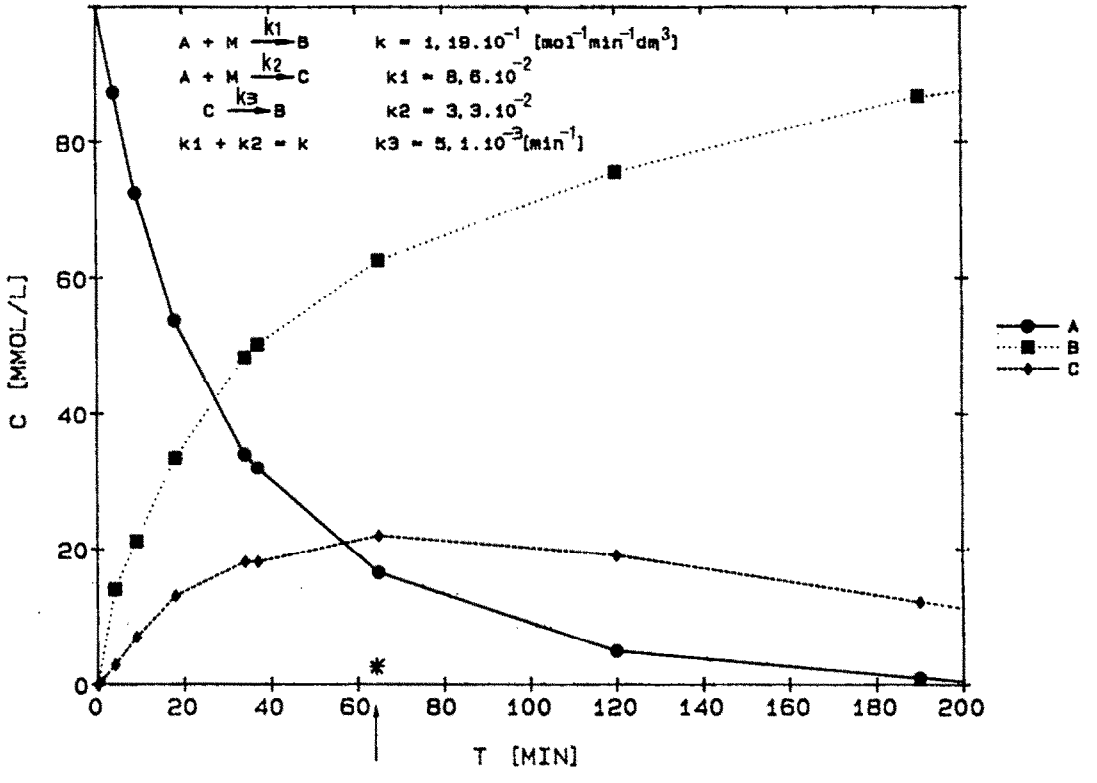


Figure 1. Reaction of 3 with CH_3SO_2Cl in d_5-pyridine at 25°C: composition of the mixture at different times: A (●) = 3, B (■) = 7, C (▲) = 5. The symbols correspond to data obtained by ^{1}H-NMR analysis.

The solution of 3 and CH_3SO_2Cl in d_5-pyridine was kept at 25° and the reaction progress examined periodically by ^{1}H-NMR spectroscopy. The changes in concentration of the individual species with time gave a plot typical for systems involving the transient formation of an intermediate (Figure 1). The appearance of signals for 7 is preceded by a transient formation of a signal at 4.13 ppm (dd, $J_{7,8}$ = 3,5 Hz $J_{7,8}$ = 13 Hz). This signal has been assigned to the 8α-H of the chlorocompound 5, which is a known by-product among reactions with CH_3SO_2Cl. There is no signal however which could be assigned to the 8α-H of the mesylate 6. Thus evi-

dence is given that the intramolecular ring closure (6→7) is much faster than the preceding formation of the mesylate (3→6). The appearance of the chlorocompound 5 indicates comparable reaction rates for both steps the chlorination (3→5) and the ring closure (5→7). This different behaviour of the chlorocompound is due to the fact that Cl^- is a less effective leaving group than $CH_3SO_2^-$.

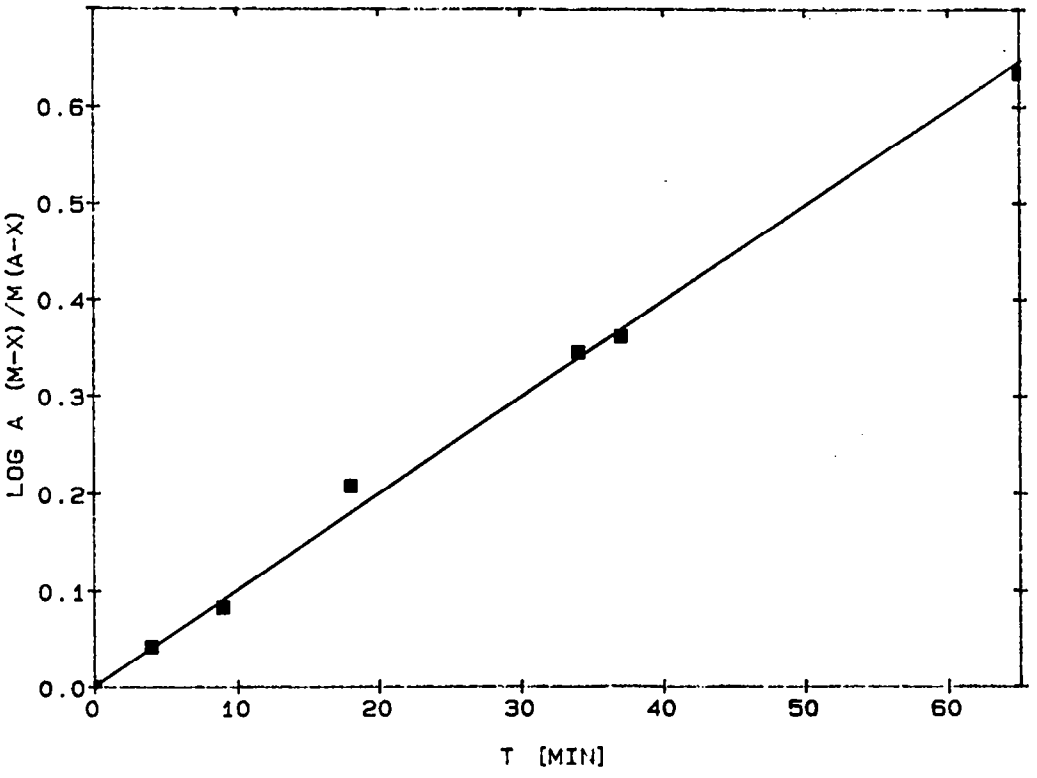


Figure 2. Second-order kinetics of the reaction of 3(A) with CH_3SO_2Cl (M) in d_5-pyridine at 25°C.

According to the plot in Figure 2 the reaction 3→6→7 exhibits second order kinetics with mesylation as the rate determining step followed by a rapid non rate determining intramolecular ring closure leading to 7. The values of the different rate constants were calculated and the results are summarized in Figure 2.

EXPERIMENTAL

Melting points were determined using a Kofler apparatus and are uncorrected. Infrared spectra were recorded on a Perkin Elmer 421 spectrometer. Electron impact mass spectra were obtained on a CH-7 Varian-MAT spectrometer. ^1H and ^{13}C NMR spectra were recorded on a Bruker WH-90 DS and WM 250 spectrometer. Chemical shifts are quoted in parts per million downfield from TMS. The ^{13}C NMR spectra were recorded at 62.90 MHz; the accumulation of the FID-signals was performed with a 32 K memory, 30° pulses and a sweepwidth of 15000 Hz were used. The following abbreviations are used: s = singlet, d = doublet, dd = doubled doublet, ddd = twice doubled doublet, dt = doubled triplet, br = broad. Microanalyses were carried out by Dr. J. Zack of the Mikroanalytisches Institut of the University of Vienna. The analytical data are in accordance (0.4% C,H,O) with the required values and are not given separately. Chromatography refers to medium pressure column chromatography using silica gel (0.05-0.2 mm Merck) and Merck columns of Type A, B and C. Yields are always based on reacted material.

3,6-Bis-(acetoxy)-4-ethyl-12-oxo-2,4,7,11-tetramethyl-7,9-ethano-1,8-propanobicyclo[6.1.0]nonane (7)

a) A solution of 0.1 ml (1.52 mmol) CH_3SO_2Cl in 2 ml CH_2Cl_2 was added at 25°C to a solution of 125 mg (0.23 mmol) 3 in 5 ml pyridine. After 1 h the reaction mixture was poured into a suspension of 0.1 n HCl and ethyl acetate. The organic layer was separated, dried over sodium sulphate and evaporated to give 110 mg of a yellowish oil. The product was purified by chromatography (silica gel, 15:1 toluene/ethyl acetate) to give 7 as a colourless oil (80 mg, 84.2 %) which crystallized from acetone hexane, m.p. 105-106°C.

b) A slurry of 40 mg 16 and 250 mg Raney-Nickel in 5 ml CH_3OH was vigorously stirred for 24 h at 25°C. The reaction mixture was then diluted with CH_3OH, filtered and evaporated. Chromatography on silica gel eluting with 20% ethyl acetate in hexane gave 16 mg (55%) 7. ^1H NMR ($CDCl_3$) 5.23 (dd, H_{14}, $J_{14,13} = 4.3$ Hz, $J_{14,13'} = 3$ Hz), 1.70 (dd, H_{13}, $J_{13,13'} = 16.5$ Hz), 1.56 (dd, $H_{13'}$), 4.87 (d, H_{11}, $J_{10,11} = 8.5$ Hz), 2.57 (m, H_{10}, $J_{10,17} = 7$ Hz), 2.03 (dd, H_8, $J_{7,8} = 7.5$ Hz, $J_{7',8} = 5.5$ Hz), 1.33 (dt, $H_{7'}$, $J_{7,7'} = 13$ Hz), 1.90 (m, H_7, $J_{6,7'} = 12.5$ Hz), 2.22 (m, H_6, $J_{6,7} = 6.5$ Hz), 2.1 (s, CH_3CO), 1.98 (s, CH_3CO), 1.58 (s, $(CH_3)_{15}$), 0.78 (s, $(CH_3)_{18}$), 0.95 (d, $(CH_3)_{17}J_{17,10} = 7.5$ Hz), 0.73 (d, $(CH_3)_{16}$, $J_{16,6} = 7.5$ Hz); IR ($CHCl_3$) 1725, 1700, 1690, 1460, 1370, 1020, 970; MS (m/e, %) 404 (M^+, 4.3), 362 (1.5), 344 (8.7), 284 (11.6), 189 (62.6), 43, 100); UV (CH_3OH) 240.5 nm (= 437).

Kinetic measurements: A solution of 16 mg (100 mmol/l) 3 (A) and 8.5 µl (283 mmol/l) CH_3SO_2Cl (M) in 0.3 ml d_5-pyridine was kept at 25°C and the reaction progress examined periodically by ^1H NMR spectroscopy (Figure 1). The reaction was followed to 95% conversion. The values of the rate constants k, k_1, k_2, k_3 were calculated from the slope of the functions log $A(M-X_t)/M(A-X_t)$ (Figure 2), B and C (Figure 1) versus time. For the caculation of k_3 was used the steady state consideration - $dC/dt = dC/dt$ at concentration * (Figure 1) as well.

4-Acetoxy-5-ethyl-9-hydroxy-3,5,8,11-tetramethyl-2,8-propanobicyclo[5.1.0]octane (8)
3-Acetoxy-6-hydroxy-4-ethyl-12-oxo-2,4,7,11-tetramethyl-7,9-ethano-1,8-propanobicyclo-[6.1.0]nonane (9)

A solution of 0.012 ml (0.15 mmol) CH_3SO_2Cl in 1 ml CH_2Cl_2 was added to a solution of 75 mg (0.15 mmol) 4 in 1 ml pyridine. After 3 min the reaction mixture was poured into a vigorously stirred suspension of 0.1 n HCl and ethyl acetate. The organic layer was separated, dried over sodium sulphate and evaporated to give 65 mg of a colourless oil. Chromatography on silica gel eluting with 15% ethyl acetate in toluene gave 9 (35 mg, 64%) and 8 (12 mg, 22%) as colourless oils which solidified after some time. 8: ^1H NMR ($CDCl_3$) 4.24 (d, H_{11}, $J_{10,11} = 8.1$ Hz), 3.85 (dd, H_8, $J_{8,7} = 3.5$ Hz, $J_{8,OH} = 12$ Hz). 9: ^1H NMR ($CDCl_3$) 4.9 (d, H_{11}, $J_{10,11} = 8.7$ Hz), 3.85 (dd, H_{14}, $J_{13,14} = 4$ Hz, $J_{13',14} = 2.5$ Hz, $J_{14,OH} = 7$ Hz), 1.42 (dd, H_{13}), 1.62 (d, H_{13}), 2.3 (m, H_6, $J_{6,7'} = 10.5$ Hz), 2.0 (dd, H_8, $J_{7,8} = J_{7,6} = 7.3$ Hz), 1.94 (dt, H_7, $J_{7,7'} = 13$ Hz), 1.25 (m, 1H, H_7, $J_{7',8} = 3.5$ Hz), 0.84 (s, $(CH_3)_{18}$), 1.48 (s, $(CH_3)_{15}$), 0.92 (d, $(CH_3)_{17}$, $J_{10,17} = 7.5$ Hz), 0.94 (d, $(CH_3)_{16}$, $J_{6,16} = 7.5$ Hz). IR(KBr) 3540, 2950, 1725, 1690, 1460, 1370, 1240 cm^{-1}; MS (m/e, %) 362 (M, 3), 302 (14.5), 261 (20.7), 189 (93.5), 162 (100).

11,14-Diacetoxy-3-oxo-8-methanesulfonyloxy-mutilan (11)

The mesylation of 10 was performed[4] (85% yield) according to the preparation of 7. ^1H NMR ($CDCl_3$) 5.64 (d, H_{14}, $J_{13,14} = 8.7$ Hz), 5.0 (d, H_{11}, $J_{10,11} = 6.5$ Hz), 4.66 (dd, H_8, $J_{7,8} = 12.5$ Hz, $J_{7',8} = 5$ Hz), 3.28 (s, CH_3SO_2), 1.88, 1.96 (s,s, 2 x CH_3CO).

11,14-Diacetoxy-3-oxo-8-fluoro-mutilan (12)

0.6 ml of Olah's HF-pyridine complex in pyridine was added to a solution of 60 mg (0.15 mmol) 7 in 5 ml CH_2Cl_2. The reaction mixture was kept 24 h at 25° and then poured into a saturated solution of sodium hydrogencarbonate. After extraction with CH_2Cl_2 the organic layer was dried over sodium sulphate and evaporated to give 85 mg of crude product. Chromatography on silica gel eluting with 10% ethyl acetate in hexane gave 12 (15 mg, 40%) and 35 mg unreacted starting material 7. ^{1}H NMR ($CDCl_3$) 5.62 (d, H_{14} $J_{13,14}$ = 7.5 Hz), 2.84 (d, H_{11}, $J_{10,11}$ = 7.5 Hz), 4.25 (ddd, H_8, J_{HF} = 45 Hz, $J_{7,8}$ = 11 Hz, $J_{7',8}$ = 5 Hz), 2.78 (q, 1H, H_{10}, $J_{10,17}$ = 7.5 Hz), 1.44 (s, $(CH_3)_{15}$), 2.0, 2.09 (s,s, 2 x CH_3CO). - IR (KBr) 2950, 1725, 1240 cm^{-1}.

11,14-Diacetoxy-3-(t-butyl-dimethyl-silyloxy)-8-thioxo-mutilen(3) (14)

A solution of 10.7 g (20 mmol) ketone 13[4] and 4.45 g (11 mmol) Lawesson's reagent[9] in 200 ml dry toluene was heated under reflux for 24 h, allowed to cool and poured into brine. The resulting suspension was extracted several times into ethyl acetate, the extracts combined, dried over sodium sulphate and evaporated to give a deeply coloured mixture of starting material and thioketone 14. Chromatography on silica gel, eluting with 15% ethyl acetate in hexane gave 14 as a purple coloured oil (5g, 57%) and starting material 13 (1.8 g). - 14: ^{1}H NMR($CDCl_3$) 5.82 (d, H_{14}, $J_{14,13}$ = 7.5 Hz), 4.78 (d, H_{11}, $J_{10,11}$ = 5.4 Hz), 3.21, 3.09 (ABX-system, H_7, $H_{7'}$, $J_{7,7'}$ = 15.5 Hz, $J_{7,6}$ = 3.1 Hz, $J_{7',6}$ = 14.6 Hz), 1.49 (s, $(CH_3)_{15}$), 0.18, 0.24 (s,s, $Si(CH_3)_2$), 0.96 (s, Si $C(CH_3)_3$), 0.78 (s, $(CH_3)_{18}$), 2.02, 2.05 (s,s, 2 x CH_3CO). - IR ($CHCl_3$) 2950, 1725, 1640 cm^{-1}. - MS (m/e, %) 550 (M, 31.6), 491 (6.7), 431 (2.1), 375 (1.52), 309 (42.6), 73 (100).

Table 1. Carbon 13-chemical shifts in ppm with respect to Me_4Si, solvent is $CDCl_3$.

Compd.No.	C_3	C_4	C_6	C_7	C_8	C_{10}	C_{11}	C_{13}	C_{14}	C_{15}	C_{16}	C_{17}	C_{18}
7	211.6	57.8	56.9	29.9	42.7	31.8	80.8	43.0	67.7	16.6	12.5	14.7	25.8
12	215.3	58.7 (8)[b]	35.8 (11)	32.9 (18)	94.0 188)	33.2	78.0	41.2	67.5	16.1	13.8	13.3	25.6
14[a]	214.9	61.7	40.7	56.3	260.0	36.0	77.1	41.2	67.7	14.3	15.7	13.6	25.4
9[a]	211.7	58.3	56.4	30.2	42.3[c]	31.9	80.7	44.8	66.3	16.0	14.7	14.5	26.2

a Assignments were made by a 2D-shift correlation between ^{13}C and H.

b Values in brackets are C-F couplings in Hz.

c $^1J_{C8}$ = 168 Hz.

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