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Total Syntheses of (±)-β-Pinguisene and (±)-Pinguisenol

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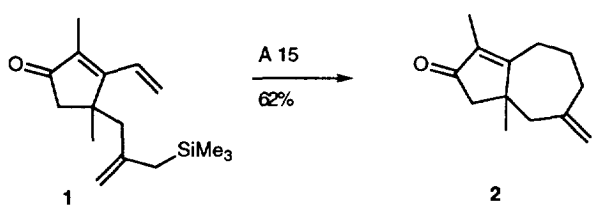
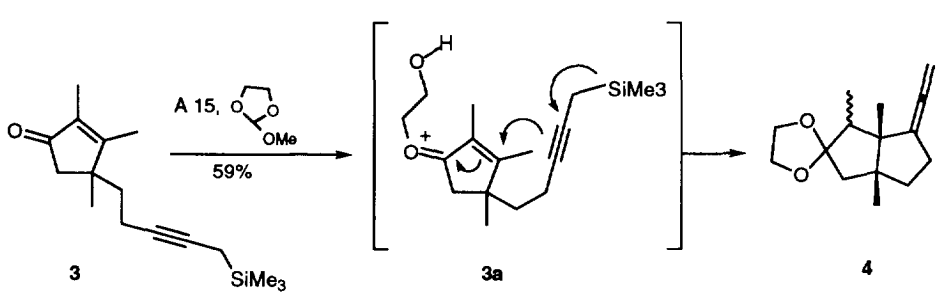
Abstract: Important ring-skeletons, such as hydroazulene **2**, bicyclooctane **4**, or hydrindanone **12** can be easily obtained by Amberlyst 15 (A 15) catalyzed cyclizations of allyl- and propargylsilanes. The total syntheses of (±)-β-pinguisene **5** and (±)-pinguisenol **6** have been achieved by propargylsilane-terminated cyclizations of enone **11** as the key step. Compound **12** was transformed in a straight forward way to provide β-pinguisene **5** and pinguisenol **6**.

In this account we wish to report a very easy synthesis of important ring-skeletons, such as hydroazulene **2** and bicyclooctane-framework **4** by simple addition of Amberlyst 15 (A 15) to the requisite allyl- or propargylsilane.[1] Two general protocols can be used for the cyclizations: stirring of the starting material, e.g. **1**, in an inert solvent such as toluene with addition of a trace of A 15.[2-4] By this technique hydroazulene **2** can be obtained, which is an important intermediate for a number of biologically active natural products, such as pseudoguaianolides.[5]



1 **2**

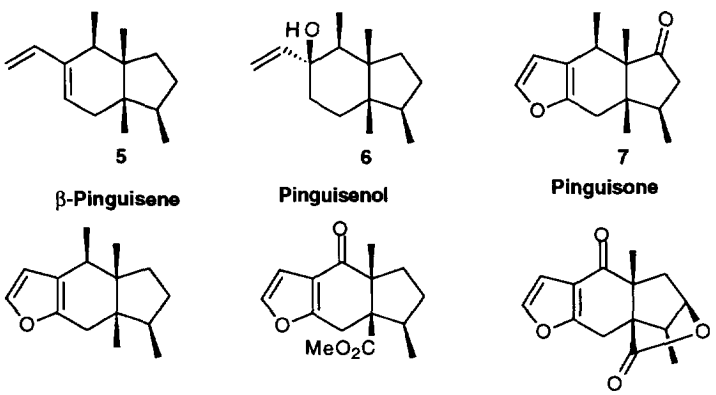
In the second protocol trans-ketalization conditions were used and methoxy-dioxolane had to be added to the reaction mixture.[2,3] In order to construct sterically hindered systems, more cationic strength is required and the ene-ketal intermediate is cleaved by A 15, forming an oxonium ion **3a**. This cation is trapped by the terminating silane providing e.g. bicyclo[3.3.0.]octane **4**. Again, compounds of type **4** are important precursors for a number of interesting natural products.[6]



3 **3a** **4**

In particular, the construction of sterically hindered systems (two or three, neightboring quaternary centers) is a major problem in annulation reactions. Sesquiterpenes of the pinguisane-type are ideal testing grounds for such annulations.

These compounds were isolated from *Porella* liverworts.[7,8] These liverworts show interesting biological activities, such as allergenic contact dermatitis[9], anticancer[10], antimicrobial[11,12], and antifeedant activities.[13] All structures have in common a bicyclo-[4.3.0]-nonane skeleton, containing several *cis* methyl groups or other functionalities.



5 β-Pinguisene

6 Pinguisenol

7 Pinguisone

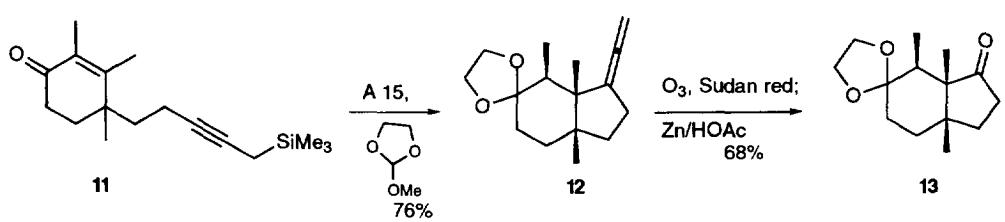
8 Deoxo-Pinguisone

9 Norpinguisone-methylester

10 Norpinguisanolide

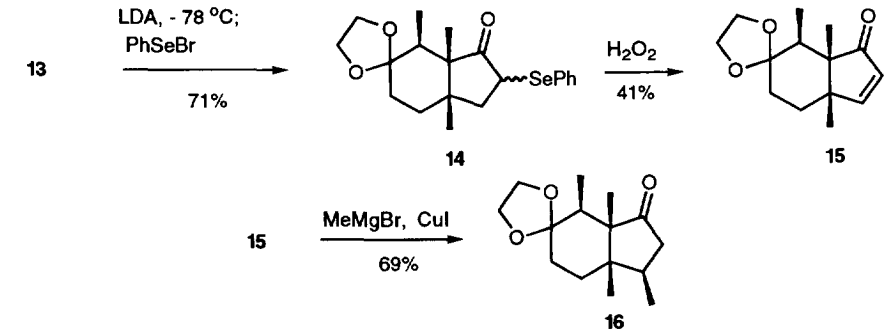
We wish to report the total syntheses of β-pinguisene **5**[4], and pinguisenol **6**, both sesquiterpene components isolated from *Porella* species.[7,8]

Compound **11** can be easily derived from a cyclic vinylogous ester using simple alkylation reactions.[14-16] Key cyclization to form **12** was achieved using the second protocol (A 15 under transketalization conditions in the presence of methoxy-dioxolane).[2-4] Compound **12** contains three neighboring β-methyl groups, of which two are quaternary centers.



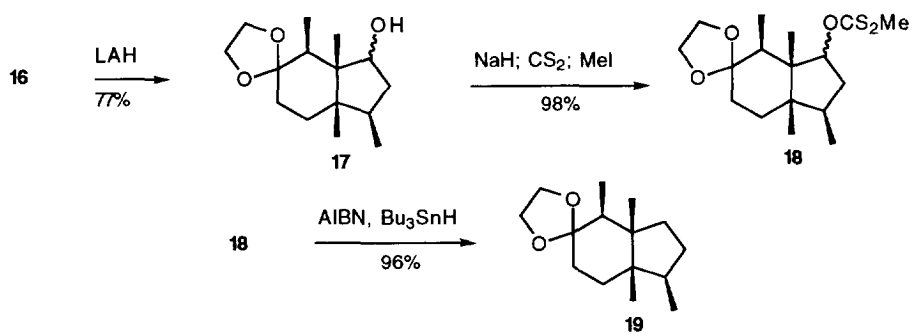
11 **12** **13**

Ozonolysis of the terminal allene with Sudan red as indicator[16] at low temperature and subsequent work-up with Zn/HOAc provided ketone **13**. Deprotonation at - 78 °C with lithium diisopropylamide (LDA) and *in situ* selenation with phenylselenyl bromide provided the selenided compound **14**, which was directly oxidized with hydrogen peroxide to give enone **15** as a single diastereomer.

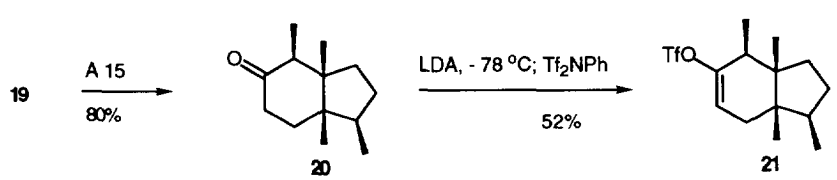


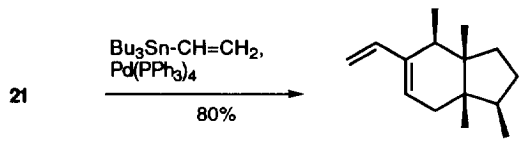
The missing methyl group was incorporated by addition of methylmagnesium bromide in the presence of copper iodide - via exo-attack - to yield compound **16** as a single diastereomer having all four methyl groups on the β-face of the molecule. The structure of **16** was confirmed by X-ray structure determination.[4]

Next, the carbonyl group in the five-membered ring had to be removed. Reduction with lithium aluminum hydride (LAH) gave alcohol **17**, which was successfully transformed into xanthogenate ester **18**. Radical-initiated cleavage in the presence of tributyltin hydride provided compound **19** in very high yield.[17]

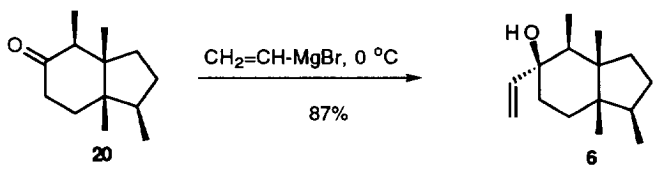


Finally, the diene moiety was incorporated. After deprotection of the ketal with A 15, a palladium-mediated cross-coupling of an enol triflate with a vinylstannane was used.[18] Deprotonation with LDA at low temperature and *in situ* trapping with *N*-phenyl-bis(trifluoromethanesulfoneimide) gave a single enol triflate **21**, which was coupled with vinylstannane in the presence of tetrakis(triphenylphosphine)palladium(0) to yield **5** as a single isomer.





Intermediate **20** was also successfully used to synthesize pinguisenol **6**. Addition of vinylmagnesium bromide in an equatorial fashion provided pinguisenol **6** as a single diastereomer, containing five neightboring, stereogenic centers.



In summary, we have shown that allyl- and propargylsilane-terminated cyclizations initiated by A 15 are powerful means of constructing various interesting ring-skeletons. The usefulness of this method has been demonstrated in the total syntheses of β-pinguisene **5** and pinguisenol **6**. Other members of this natural product family are currently being synthesized in our laboratories.

Acknowledgment. This work was supported by the Deutsche Forschungsgemeinschaft (DFG) and the Fonds der Chemischen Industrie. We are indebted to Schering AG, Berlin, for generous gifts of chemicals.

Experimental Part

High resolution mass spectra were obtained on Finnigan MAT 312 and MAT 8430 spectrometers. IR spectra were recorded on a Perkin-Elmer 580, FT 1710 and Nicolet 320 FT-IR spectrometers. NMR spectra were recorded on Bruker WH 200 and WH 400 spectrometers.
All organometallic reactions were run under nitrogen, and pure products were obtained after flash chromatography using the solvent system ethyl acetate/petroleum ether (EE/PE), PE boiling range 40-65 °C. Additions were carried out using a syringe pump. All compounds obtained are racemates.

7,10-Dimethyl-5-methylen-bicyclo[3.5.0]dec-10-ene-9-one 2

To a solution of 100 mg (0.38 mmol) **1** in 1 ml toluene is added 10 mg A 15 at room temperature. The mixture is stirred for 72 h at room temperature and is poured into 20 ml of ether. The catalyst is filtered away and the solvent is removed under reduced pressure. The crude product is flash chromatographed with EE/PE (1:9) to yield 45 mg (0.236 mmol; 62%) of pure product **2** as a colourless oil.
General Data: $C_{13}H_{18}O$, MW = 190.29, R_f = 0.18 (EE/PE 1:9).

^{1}H-NMR ($CDCl_3$): δ = 1.06 (s, 3H, H-11), 1.23-1.35 (m, 1H), 1.52 (s, 3H, H-12), 1.84-1.92 (m, 1H), 2.04-2.26 (m, 7H), 2.62 (ddd, 1H, J = 13.35 Hz, J = 6.35 Hz, J = 3.16 Hz), 4.62 (d, 2H, H-13, J = 27.71 Hz).

^{13}C-NMR ($CDCl_3$): δ = 208.63 (s, C-9), 180.48 (s, C-1), 145.96 (s, C-5), 134.52 (s, C-10), 113.96 (t, C-13), 49.36, 46.54, 38.04, 27.75, 26.69 (t, C-2, C-3, C-4, C-6, C-8), 43.96 (s, C-7), 27.70 (q, C-12), 7.63 (q, C-11).
MS (EI, 70 eV): m/z (%) = 190 (100) [M$^+$], 175 (26), 162 (38), 147 (43), 135 (30), 107 (23), 105 (24), 91 (36), 79 (30), 65 (8).
High Resolution MS: calcd.: 190.1357; found: 190.1357

IR (Film): ν = 2928 (s), 2866 (s), 1722 (m), 1699 (vs), 1642 (s), 1451 (m), 1409 (m), 1384 (m), 1334 (m), 1079 (m), 1066 (m), 897 (m), 639 (m).

1,5,8 Trimethyl-2-vinylidene-7-spiro-2',5'-dioxa-bicyclo[3.3.0]octane 4

To a solution of 100 mg (0.38 mmol) of **3** in 2 ml of toluene is added 0.19 ml (1.89 mmol) of 2-methoxy-1,3-dioxolane and 30 mg A 15 at room temperature. The mixture is stirred for 24 h at room temperature and is poured into 20 ml of ether. The solvent is removed under reduced pressure and the crude product is flash chromatographed with EE/PE (1:9) to yield 52 mg (0.222 mmol; 58%) of pure product **4** as a colourless oil and a 2:1 mixture of diastereomers.
General Data: $C_{15}H_{22}O_2$, MW = 234.34, R_f = 0.56 (EE/PE 1:9).

^{1}H-NMR ($CDCl_3$): δ = 0.73/0.75 (s, 3H, H-11), 0.81/0.82 (s, 3H, H-10), 0.85/0.95 (d, 3H, H-9, J = 11.98 Hz), 1.39-1.56 (m, 2H), 1.65 (d, 1H, J = 14,04 Hz), 1.72 (d, 1H, J = 11.07 Hz), 1.77-1.86 (m, 1H), 2.16 (q, 1H, J = 7.15Hz), 2.40-2.45 (m, 1H), 3.67-3.83 (m, 4H, H-14, H-15), 4.54-4.72 (m, 2H, H-13).

^{13}C-NMR ($CDCl_3$): δ = 203.91/202.86 (s, C-12), 111.31 (s, C-7), 108.99 (s, C-2), 76.86/76.19 (t, C-13), 65.12/64.89, 64.26/64.13 (t, C-14, C-15), 54.89/54.10 (s, C-1), 51.72/50.48 (d, C-8), 51.21/49.50 (t, C-3), 48.91 (s, C-5), 39.68/38.74 (t, C-6), 27.59/26.86 (t, C-4), 22.96/22.76 (q, C-11), 14.32/14.05 (q, C-10), 8.37/7.37 (q, C-9).
MS (EI, 70 eV): m/z (%) = 234 (62) [M$^+$], 219 (62), 205 (12), 189 (12), 175 (18), 163 (17), 147 (33), 133 (100), 119 (38), 105 (50), 91 (44), 77 (20), 55 (22).
High Resolution MS: calcd.: 234.1619; found: 234.1619

IR (Film): ν = 2958 (s), 2927 (s), 2875 (s), 1958 (m), 1455 (m), 1381 (m), 1317 (m), 1149 (m), 1117 (m), 1079 (m), 1063 (s), 950 (m), 843 (m).

1,5,9-Trimethyl-2-vinylidene-8-spiro-2',5'-doxa-bicyclo[4.3.0]nonane 12

To 2.47 g (8.95 mmol) of **11** was added 4.25 ml (44.75 mmol) of 2-methoxy-1,3-doxolane in the presence of 200 mg of A 15. The mixture was stirred overnight at room temperature and was poured into 50 ml of ether. The catalyst was filtered away and the solution was evaporated under reduced pressure. The crude product was flash chromatographed with ethyl acetate/petroleum ether (1:9) to yield 1.64 g (6.6 mmol) of pure product **12** (74%).
General data: $C_{16}H_{24}O_2$, MW = 248.37, R_f = 0.52 (EE/PE 1:9).

^{1}H-NMR ($CDCl_3$): δ = 0.84 (d, 3H, H-10, J = 6.84 Hz), 0.85 (s, 3H, H-11), 0.90 (s, 3H, H-12), 1.17-1.24 (m, 1H), 1.44-1.48 (m, 1H), 1.59-1.69 (m, 3H), 1.85 (q, 1H, H-9, J = 6.82 Hz), 2.13 (dd, 1H, J = 22.61 Hz, J = 10.05 Hz), 2.45-2.53 (m, 2H), 3.78-4.04 (m, 4H, H-15, H-16), 4.73 (dq, 2H, H-14, J = 32.23 Hz, J = 4.52 Hz).

^{13}C-NMR ($CDCl_3$):δ = 204.35 (s, C-13), 111.16 (s, C-8), 110.68 (s, C-2), 76.55 (t, C-14), 65.44, 64.08 (t, C-15, C-16), 51.82 (s, C-1), 44.33 (s, C-5), 41.87 (d, C-9), 32.02, 30.82, 30.11, 25.54 (t, C-3, C-4, C-6, C-7), 26.11 (q, C-12), 13.35 (q, C11), 7.63 (q, C-10).
MS (EI, 70 eV): m/z (%) = 248 (3.5) [M$^+$], 233 (0.8), 219 (1.6), 191 (1.3), 166 (2.5), 147 (2.6), 133 (1.3), 119 (2), 99 (100), 86 (12), 67 (6), 55 (10), 43 (3).
High Resolution MS: calcd.: 248.177; found: 248.177

IR (Film): ν = 2978 (s), 2953 (vs), 2881 (s), 1958 (m), 1458 (m), 1373 (m), 1349 (m), 1322 (m), 1286 (m), 1226 (m), 1175 (s), 1151 (m), 1104 (s), 1094 (s), 1067 (vs), 1003 (m), 936 (m), 897 (m), 842 (s), 735 (m), 647 (m).

1,5,9-Trimethyl-8-spiro-2',5'-dioxa-bicyclo[4.3.0]nonane-2-one 13

A steam of ozone is bubbled into a cooled solution (-78 °C) containing 700 mg (2.82 mmol) of **12** and 0.4 ml of pyridine in 45 ml of dichloromethane (0.1 ml of a saturated solution of Sudan Red in dichloromethane was employed as an indicator). Ozone is bubbled into the solution until the colour of the indicator has disappeared. Nitrogen is bubbled into the mixture for additional 15 min. The solution is then poured into a flask containing zinc dust (1.4 g). Acetic acid (3.99 ml) is added, and the mixture is allowed to warm to room temperature and stirred for 1 h. The mixture is filtered through Celite and washed with water (3 x 50 ml), 5% aqueuos NaOH (3 x 75 ml), and water (3 x 50 ml) until neutral to litmus. The solution is extracted with 100 ml of dichloromethane, dried with $MgSO_4$, and concentrated under reduced pressure. The crude product is flash-chromatographed with ethyl acetate/petroleum ether (2:8) to yield 457 mg (68%) of pure compound **13** (white crystalls).
General Data: $C_{14}H_{22}O_3$, F_p = 44 °C, MW = 238.33, R_f = 0.51 (EE/PE 2:8).

^{1}H-NMR ($CDCl_3$): δ = 0.77 (d, 3H, H-10), 0.84 (s, 3H, H-11), 0.85 (s, 3H, H-12), 1.20-1.24 (m, 1H), 1.37-1.44 (m, 1H), 1.50-1.54 (m, 1H), 1.63-1.71 (m, 2H), 1.85(q, 1H, H-9, J = 6.94 Hz), 2.15-2.26 (m, 2H), 2.37-2.46 (m, 1H), 3.85-4.00 (m, 4H, H-13, H-14).

^{13}C-NMR ($CDCl_3$):δ = 219.17 (s, C-2), 109.88 (s, C-8), 65.34, 64.05 (t, C-13, C-14), 55.89 (s, C-1), 41.24 (s, C-5), 37.30 (d, C-9), 33.64 (t, C-3), 31.42 (t, C-7), 30.15 (t, C-4), 28.73 (t, C-6), 25.64 (q, C-12), 11.06 (q, C-11), 7.94 (q, C-10).
MS (EI, 70 eV): m/z (%) = 238 (5) [M$^+$], 223 (0.4), 193 (0.4), 181 (0.7), 167 0.8), 151 (0.9), 140 (1.3), 123 (0.5), 99 (100), 86 (8), 73 (7), 55 (8), 43 (3).

IR (KBr): ν = 2956 (s), 2927 (s), 2892 (s), 1736 (s), 1459 (m), 1440 (m), 1385 (m), 1378 (m), 1350 (m), 1267 (m), 1228 (m), 1177 (m), 1103 (m), 1072 (s), 1003 (m), 918 (m), 857 (m), 841 (m), 734 (s), 647 (m).
Analysis calcd for: $C_{14}H_{22}O_3$ (238.33): calcd: C 70.56; H 9.30; found:C 70.68; H 9.51

1,5,9-Trimethyl-8-spiro-2',5'-dioxa-3-(phenylseleno)-bicyclo[4.3.0]nonane-2-one 14

To a solution of 1.36 ml (9.66 mmol) diisopropyl amine in 50 ml THF is added at 0 °C 6.04 ml (1.6 mmol) of butyllithium (1.6 M in hexane). The mixture is stirred for 10 min, cooled to - 78 °C, and 1.15 g (4.83 mmol) of **13** in 3 ml of THF is added within 1 h by a syringe pump. After stirring for 1 h at low temperature, a solution of 2.28 g (9.66 mmol) of phenylselenium bromide in 2 ml of THF is added. The mixture is allowed to warm to room temperature and is quenched with 20 ml of saturated NH_4Cl solution, extracted twice with 20 ml of ether, and is dried with $MgSO_4$. The crude product is flash chromatographed with ethyl acetate/petroleum ether (1:9) to yield 1.34 g (3.41 mmol) of pure **14** (71%) as a 1:4 mixture of 2 diastereomers.
General Data: $C_{20}H_{26}O_3Se$, F_p = 42 °C, MW = 393.39, R_f = 0.31 (EE/PE 1:9).

^{1}H-NMR ($CDCl_3$): δ = 0.71/0.75 (d, 3H, H-10, J = 6.68 Hz), 0.83/0.84 (s, 3H, H-11), 0.89/0.93 (s, 3H, H-12), 1.25-1.32 (m, 2H), 1.39-1.45 (m, 2H), 1.60 (dd, 1H, J = 5.23 Hz, J = 2.09 Hz), 1.74 (q, 1H, H-9, J = 6.77 Hz), 1.84 (dd, 1H, J = 13.55 Hz, J = 9.20 Hz), 2.31 (dd, 1H, J = 13.51 Hz, J = 10.16 Hz), 3.74-3.98 (m, 4H, H-13, H-14), 7.27-7.36 (m, 3H, H-4``, H-3``), 7.63-7.67 (m, 2H, H-2``).

^{13}C-NMR ($CDCl_3$): δ = 217.05/217.02 (s, C-2), 136.80/134.90 (d, C-2``), 128.89/128.67 (d, C-3``), 128.70 (s, C-1``), 128.03/128.02 (d, C-4``), 109.49/109.46 (s, C-8), 65.33/65.23, 64.16/64.07 (t, C-13, C-14), 56.65/55.93 (s, C-1), 41.91 (d, C-3), 40.89/40.67 (s, C-5), 37.13 (t, C-4), 37.13 (d, C-9), 31.39/30.79 (t, C-7), 30.52/30.32 (t, C-6), 26.07 (q, C-12), 11.27/10.04 (q, C-11), 7.33/7.00 (q, C-10).
MS (EI, 70 eV): m/z (%) = 394 (8) [M$^+$], 314 (4), 248 (4), 237 (6), 214 (3), 195 (4), 155 (4), 123 (4), 99 (100), 86 (6), 73 (8), 55 (8), 43 (6).
High Resolution MS: calcd.: 394.104; found: 394.104

IR (KBr): ν = 2987 (m), 2957 (s), 2937 (s), 2929 (s), 2907 (s), 2884 (m), 1735 (vs), 1477 (m), 1458 (s), 1437 (m), 1386 (m), 1351 (m), 1270 (m), 1167 (s), 1095 (s), 1063 (vs), 1004 (m), 954 (m), 940 (s), 899 (m), 738 (s), 692 (s).

1,5,9-Trimethyl-8-spiro-2',5'-dioxa-bicyclo[4.3.0]non-3-ene-2-one 15

To a solution of 1.30 g (3.31 mmol) **14** in 10 ml of dichloromethane is added via syringe pump over 1 h 0.15 ml of H_2O_2 (35% solution) at room temperature. The mixture is stirred for 1 h at room temperature, 10 ml of a saturated solution of $NaHCO_3$ is added, the mixture is extracted twice with 20 ml of dichloromethane, and dried with $MgSO_4$. The crude product is flash chromatographed with ethyl acetate/petroleum ether (3:7) to yield 320 mg (41%) of pure compound **15** (white crystalls).

General Data: $C_{14}H_{20}O_3$, F_p = 39 °C, MW = 236.31, R_f = 0.41 (EE/PE 3:7).

^{1}H-NMR ($CDCl_3$): δ = 0.86 (d, 3H, H-10, J = 6.94 Hz), 0.98 (s, 3H, H-11), 1.00 (s, 3H, H-12), 1.37-1.44 (m, 1H), 1.64-1.69 (m, 1H), 1.70-1.75 (m, 2H), 1.85 (q, 1H, H-9, J = 7.02 Hz), 3.79-3.94 (m, 4H, H-13, H-14), 5.95 (d, 1H, H-4, J = 5.76 Hz), 7.31 (d, 1H, H-3, J = 5.76 Hz).

^{13}C-NMR ($CDCl_3$): δ = 212.76 (s, C-2), 168.87 (d, C-3), 129.07 (d, C-4), 110.53 (s, C-8), 65.64, 63.94 (t, C-13, C-14), 55.21 (s, C-1), 47.96 (s, C-5), 41.56 (d, C-9), 32.16 (t, C-7), 31.71 (t, C-6), 28.30 (q, C-12), 11.37 (q, C-11), 8.30 (q, C-10).
MS (EI, 70 eV) m/z (%) = 236 (0.4) [M$^+$], 221 (0.2), 207 (1.2), 192 (0.9), 177 (0.6), 163 (0.7), 145 (1.5), 137 (4.5), 125 (8), 99 (100), 86 (10), 77 (4), 67 (4), 55 (8), 43 (4).

IR (KBr):ν = 2982 (s), 2960 (s), 2935 (s), 2878 (s), 1705 (vs), 1459 (s), 1443 (m), 1382 (m), 1335 (m), 1292 (m), 1179 (m), 1166 (s), 1143 (m), 1106 (m), 1091 (s), 1071 (vs), 1029 (m), 1020 (m), 954 (m), 908 (m), 853 (m).
Elemetal Analysis calcd. for: $C_{14}H_{20}O$ (236.31): calcd.: C 71.16; H 8.53; found: C 70.69; H 8.72

1,4,5,9-Tetramethyl-8-spiro-2',5'-dioxa-bicyclo[4.3.0]nonane-2-one 16

To a mixture of 336 mg (1.76 mmol) of CuI in 10 ml of ether is added at 0 °C 1.18 ml (3.53 mmol) of a 3.0 M solution of methylmagnesium bromide in ether over 30 min. After additional stirring of 30 min at the same temperature 320 mg (1.36 mmol) **15** is added over a period of 20 min. The reaction mixture is stirred for an additional h at the same temperature and the mixture is poured into 100 ml of saturated NH_4Cl solution, washed with 50 ml of brine, extracted twice with 50 ml of ether, dried with $MgSO_4$, and concentrated under reduced pressure. The crude product is flash-chromatographed with ethyl acetate/petroleum ether (3:7) to yield 236 mg (0.94 mmol; 69%) of pure product **16**.
General Data: $C_{15}H_{24}O_3$, MW = 252.36, R_f = 0.51 (EE/PE 3:7).

^{1}H-NMR ($CDCl_3$): δ = 0.63 (s, 3H, H-11), 0.74 (d, 3H, H-10, J = 6.85 Hz), 0.86 (s, 3H, H-12), 0.92 (d, 3H, H-13, J = 6.64 Hz), 1.50 (dd, 1H, J = 14.04 Hz, J = 4.61 Hz), 1.54-1.61 (m, 2H), 1.64 (dd, 1H, J = 13.90 Hz, J = 4.71 Hz), 1.79 (dd, 1H, J = 18.95 Hz, J = 10.74 Hz), 1.95 (q, 1H, H-9, J = 6.83 Hz), 2.54 (dd, 1H, J = 19.34 Hz, J = 9.07 Hz), 2.63-2.71 (m, 1H), 3.71-4.00 (m, 4H, H-14, H-15).

^{13}C-NMR ($CDCl_3$): δ = 219.68 (s, C-2), 109.70 (s, C-8), 65.51, 64.30 (t, C-14, C-15), 57.61 (s, C-1), 43.66 (s, C-5), 41.90 (t, C-3), 36.73 (d, C-9), 30.46 (t, C-7), 29.40 (d, C-4), 27.88 (t, C-6), 19.06 (q, C-12), 13.78 (q, C-13), 10.30 (q, C-11), 7.14 (q, C-10).
MS (EI, 70 eV): m/z (%) = 252 (0.7) [M$^+$], 238 (0.6), 193 (0.2), 177 (1.3), 161 (4), 148 (1.1), 135 (3), 110 (70), 95 (100), 79 (8), 67 (12), 55 (18), 43 (10).
High Resolution MS: calcd.: 252.172; found: 252.172

IR (Film): ν = 2965 (s), 2952 (s), 2882 (s), 1733 (vs), 1459 (m), 1380 (m), 1243 (m), 1178 (s), 1106 (m), 1074 (vs), 1043 (m), 1007 (m), 918 (m).

1,4,5,9.Tetramethyl-8-spiro-2',5'-dioxa-bicyclo[4.3.0]nonane-2-ol 17

To a slurry of 34.8 mg (0.92 mmol) of lithium aluminum hydride in 9 ml ether is added 210 mg of **16** in 2 ml ether over a period of 20 min. The mixture is refluxed for 30 min, cooled to room temperature and is hydrolized in ice water. The mixture is extracted twice with 10 ml of ether, washed with 10 ml of brine, and is dried with $MgSO_4$. The crude product is flash-chromatographed with EE/PE (3:7) to yield 210 mg (0.825 mmol; 99%) of pure compound **17** as a 1:1 mixture of diastereomers.
General Data: $C_{15}H_{26}O_3$, MW = 254.37, R_f = 0.32 (EE/PE 3:7).

^{1}H-NMR ($CDCl_3$): δ = 0.69/0.77 (s, 3H, H-11), 0.84 (d, 3H, H-10, J = 2.34 Hz), 0.86 (d, 3H, H-13, J = 2.31 Hz), 0.92/1.01 (s, 3H, H-12), 1.23-1.30 (m, 2H), 1.35-1.46 (m, 2H), 1.52-1.55 (m, 2H), 1.61 (q, 1H, H-9, J = 6.82 Hz), 2.01-2.29 (m, 1H), 2.39-2.46 (dt, 1H, J = 14.01 Hz, J = 8.29 Hz), 3.76-4.03 (m, 4H, H-14, H-15).

^{13}C-NMR ($CDCl_3$): δ = 111.69/110.90 (s, C-8), 82.89/77.57 (d, C-2), 65.38/65.31, 64.12/63.96 (t, C-14, C-15), 52.29/49.67 (s, C-1), 45.22/44.40 (s, C-5), 41.28/39.34 (t, C-3), 41.20/37.87 (d, C-9), 33.92/32.01 (d, C-4), 30.13/30.04 (t, C-7), 29.14/29.11 (t, C-6), 19.91/19.31 (q, C-12), 14.68/14.06 (q, C-13), 10.47/9.96 (q, C-11), 8.49/8.45 (q, C-10).
MS (EI, 70 eV): m/z (%) = 254 (8) [M$^+$], 238 (4), 210 (4), 169 (14), 153 (12), 137 (28), 125 (42), 99 (100), 81 (14), 67 (12), 55 (12), 43 (28).
High Resolution MS: calcd.: 254.1881; found: 254.1873

IR (Film): ν = 3449 (s), 3444 (s), 2952 (vs), 2938 (vs), 2880 (vs), 1460 (s), 1377 (m), 1349 (m), 1283 (m), 1224 (m), 1177 (s), 1158 (m), 1133 (s), 1093 (s), 1070 (vs), 1039 (s), 1012 (m), 948 (m), 913 (s), 734 (m), 640 (m).

Dithiocarboxylic-acid-2-O-(1,4,5,9-tetramethyl-8-spiro-2',5'-dioxa-bicyclo[4.3.0]nonyl)-S-methylester 18

To a slurry of 66 mg (1.65 mmol) NaH (65% suspension in mineral oil) in 10 ml THF is added 210 mg (0.83 mmol) **17** in 2 ml of ether over a period of 15 min. The mixture is stirred for 1 h at room temperature and 0.07 ml (0.83 mmol) carbon disulfide is added. The mixture is warmed to 50 °C for 1 h and 0.07 ml (1.08) of methyl iodide is added. After stirring for an additional h the mixtures is poured into 20 ml of water, extracted twice with 30 ml ether, washed with brine, and is dried with $MgSO_4$. The solvent is removed under reduced pressure and the crude product is flash chromatographed with EE/PE (3:7) to yield 280 mg (0.81 mmol, 98%) of pure product **18** as a 1:1 mixture of diastereomers.
General Data: $C_{17}H_{28}O_3S_2$, MW = 344.54, R_f = 0.67 (EE/PE 3:7).

^{1}H-NMR ($CDCl_3$): δ = 0.74/0.80 (s, 3H, H-11), 0.81/0.93 (d, 3H, H-10, J = 6.83 Hz), 0.86/0.99 (d, 3H, H-13, J = 6.69 Hz), 0.89/1.01 (s, 3H, H-12), 1.34-1.61 (m, 5H), 1.72 (q, 1H, H-9, J = 6.79 Hz), 1.79-1.88 (m, 1H), 1.94-2.10 (m, 1H), 2.29 (d, 1H, J = 6.46 Hz), 2.54 (s, 3H, H-17), 3.76-3.98 (m, 4H, H-14, H-15).

^{13}C-NMR ($CDCl_3$): δ = 216.10/214.62 (s, C-16), 111.32/110.60 (s, C-8), 93.46/89.60 (d, C-2), 65.47/65.39, 64.14/64.06 (t, C-14, C-15), 53.76/50.94 (s, C-1), 45.48/44.94 (s, C-5), 40.61 (q, C-17), 38.63 (d, C-9), 38.59/35.94 (t, C-3), 34.14/32.81 (d, C-4), 30.00/29.68 (t, C-7), 28.68/28.65 (t, C-6), 19.69/19.16 (q, C-12), 14.20/14.07 (q, C-13), 10.75/10.26(q, C-11), 8.78 (q, C-10).
MS (EI, 70 eV): m/z (%) = 344 (0.5) [M$^+$], 300 (0.7), 281 (0.3), 267 (2), 237 (20), 193 (10), 175 (24), 157 (14), 138 (14), 121 (14), 109 (18), 99 (100), 86 (8), 69 (12), 55 (16), 41 (8).
High Resolution MS: calcd.: 344.147; found: 344.147

IR (Film): ν = 2956 (s), 2926 (s), 2877 (s), 1715 (m), 1459 (m), 1381 (m), 1276 (m), 1238 (vs), 1213 (vs), 1191 (m), 1178 (m), 1147 (m), 1093 (s), 1070 (vs), 1059 (vs), 1028 (s), 1008 (m), 949 (m), 919 (m), 911 (m).

1,4,5,9-Tetramethyl-8-spiro-2',5'-dioxa-bicyclo[4.3.0]nonane 19

To a solution of 300 mg (0.87 mmol) **18** in 17 ml of benzene is added a trace of AIBN. The mixture is refluxed for 30 min and 0.58 ml (2.18 mmol) tributyltin hydride in 3 ml of benzene is added in 30 min via syringe pump. The mixture is refluxed for an additional h, cooled to room temperature, 10 ml of a saturated solution of NaF is added, and the mixture is stirred at room temperature for an additional 30 min. The reaction mixture is extracted twice with 30 ml ether, washed with brine, and dried with $MgSO_4$. The solvent is removed under reduced pressure and the crude product is flash chromatographed with EE/PE (3:7) to yield 199 mg (0.834 mmol; 99%) of pure product **19**.
General Data: $C_{15}H_{26}O_2$, MW = 238.37, R_f = 0.77 (EE/PE 3:7).

^{1}H-NMR ($CDCl_3$): δ = 0.61 (s, 3H, H-11), 0.79 (d, 3H, H-10, J = 6.85 Hz), 0.81 (d, 3H, H-13, J = 6.84 Hz), 0.83 (s, 3H, H-12), 1.17-1.24 (m, 2H), 1.28 (dd, 1H, J = 12.02 Hz, J = 5.56 Hz), 1.33-1.42 (m,

2H), 1.51 (t, 1H, J = 4.11 Hz), 1.55-1.60 (m, 1H), 1.63 (dd, 1H, J = 13.13 Hz, J = 3.60 Hz), 1.83 (q, 1H, H-9, J = 6.76 Hz), 2.30-2.41 (m, 1H), 3.72-3.98 (m, 4H, H-14, H-15).

^{13}C-NMR ($CDCl_3$): δ = 111.37 (s, C-8), 65.33, 63.95 (t, C-14, C-15), 48.87 (s, C-1), 44.89 (s, C-5), 41.42 (d, C-9), 35.61 (t, C-7), 35.01 (d, C-4), 30.35, 29.01, 28.30 (t, C-2, C-3, C-6), 18.85 (q, C-12), 16.64 (q, C-13), 14.68 (q, C-11), 8.22 (q, C-10).
MS (EI, 70 eV): m/z (%) = 238 (1.2) [M^+], 223 (0.4), 193 (0.2), 179 (0.5), 153 (3), 140 (0.8), 127 (0.6), 99 (100), 86 (10), 69 (3), 55 (4), 41 (4).
High Resolution MS: calcd.: 238.193; found: 238.193

IR (Film): ν = 2958 (s), 2951 (s), 2873 (s), 1471 (m), 1440 (m), 1383 (m), 1349 (m), 1226 (m), 1182 (m), 1168 (m), 1101 (s), 1067 (s), 1025 (m), 913 (s), 735 (m), 647 (m).

1,4,5,9-Tetramethyl-bicyclo[4.3.0]nonan-8-one 20

To a solution of 110 mg (0.46 mmol) **19** in 4 ml of dichloromethane is added 0.1 ml water and 70 mg A 15 and the mixture is stirred for 24 h. The mixture is poured into 50 ml of ether, the catalyst is filtered away, and the solvent is removed under reduced pressure. The crude product is flash chromatographed with EE/PE (3:7) to yield 69 mg (0.355 mmol; 77%) of pure product **20**.
General Data: $C_{13}H_{22}O$, MW = 194.32, R_f = 0.66 (EE/PE 3:7).

^{1}H-NMR ($CDCl_3$): δ = 0.68 (s, 3H, H-11), 0.69 (s, 3H, H-12), 0.90 (d, 3H, H-13, J = 1.65 Hz), 0.92 (d, 3H, H-10, J = 1.47 Hz), 1.27-1.43 (m, 3H), 1.58 (ddd, 1H, J = 14.21 Hz, J = 12.65 Hz, J = 5.10 Hz), 1.65-1.72 (m, 1H), 1.80-1.94 (m, 1H), 2.12 (ddd, 1H, J = 14.25 Hz, J = 5.11 Hz, J = 3.95 Hz), 2.38-2.53 (m, 2H), 2.56 (q, 1H, H-9, J = 6.57 Hz).

^{13}C-NMR ($CDCl_3$):δ = 214.29 (s, C-8), 53.28 (s, C-1), 48.29 (d, C-9), 45.54 (s, C-5), 37.42 (d, C-4), 37.42 (t, C-7), 35.33, 32.30, 29.04 (t, C-2, C-3, C-6), 18.33 (q, C-12), 16.47 (q, C-13), 14.85 (C-11), 8.70 (q, C-10).
MS (EI, 70 eV): m/z (%) = 194 (18) [M^+], 179 (30), 161 (14), 152 (10), 147 (6), 137 (18), 123 (42), 109 (100), 95 (26), 81 (28), 67 (28), 55 (24), 41 (20).
High Resolution MS: calcd.: 194.1670; found: 194.1666

IR (Film): ν = 2966 (vs), 2961 (vs), 2874 (s), 1739 (m), 1714 (vs), 1470 (m), 1457 (m), 1436 (m), 1380 (s), 1352 (m), 1241 (m), 1139 (m), 1067 (m), 1010 (m).

Triflouromethanesulfonic-acid-8-(1,4,5,9-tetramethyl-bicyclo[4.3.0]non-8-enyl)ester 21

To a solution of 0.05 ml (0.37 mmol) diisopropyl amine in 2 ml THF is added at 0 °C 0.15 ml (0.37 mmol) of butyllithium (2.5 M in hexane). The mixture is stirred for 10 min, cooled to - 78 °C, and 60 mg (0.31 mmol) of **20** in 2 ml of THF is added within 1 h by a syringe pump. After stirring for 1 h at low temperature, a solution of 122 mg (0.34 mmol) of N-phenylbis(trifluoromethanesulfone amide) in 2 ml of THF is added. The mixture is allowed to warm to room temperature overnight and is quenched with 20 ml of saturated NH_4Cl solution, extracted twice with 20 ml of ether, and is dried with $MgSO_4$. The crude product is flash chromatographed with EE/PE (3:7) to yield 52 mg (0.16 mmol) of pure **21** (52%).
General Data: $C_{14}H_{21}F_3O_3S$, MW = 326.38, R_f = 0.34 (PE).

^{1}H-NMR ($CDCl_3$): δ = 0.70 (s, 3H, H-11), 0.78 (s, 3H, H-12), 0.84 (d, 3H, H-13, J = 6.62 Hz), 1.05 (d, 3H, H-10, J = 7.22 Hz), 1.19-1.28 (m, 2H), 1.34-1.43 (m, 1H), 1.52-1.59 (m, 1H), 1.86-1.95 (m, 1H), 2.02 (dd, 1H, J = 6.71 Hz, J = 2.56 Hz), 2.09 (ddd, 1H, J = 18.92 Hz, J = 5.33 Hz, J = 2.64 Hz), 2.45-2.51 (m, 1H), 5.55-5.58 (m, 1H, H-7).

^{13}C-NMR ($CDCl_3$): δ = 150.49 (s, C-8), 116.92 (s, C-14), 115.74 (d, C-7), 48.39 (s, C-1), 44.25 (s, C-5), 37.08 (d, C-9), 36.84 (d, C-4), 33.83 (t, C-6), 30.50, 28.54 (t, C-2, C-3), 18.10 (q, C-12), 14.88 (q, C-13), 14.47 (q, C-11), 11.95 (q, C-10).
MS (EI, 70 eV): m/z (%) = 326 (1.5) [M^+], 311 (1), 281 (1.1), 255 (0.4), 238 (1), 225 (0.4), 177 (1.6), 161 (4), 110 (98), 95 (100), 81 (8), 67 (10), 55 (14), 43 (4).
High Resolution MS: calcd.: 326.116; found: 326.116

IR (Film): ν = 2977 (s), 2962 (s), 2878 (s), 1455 (m), 1448 (m), 1417 (s), 1386 (m), 1246 (s), 1210 (vs), 1145 (s), 1039 (m), 1020 (m), 985 (s), 881 (s), 832 (m), 670 (m), 620 (s).

1,4,5,9-Tetramethyl-8-vinyl-bicyclo[4.3.0]non-8-ene [(±)-β-Pinguisene] 5

To a solution of 30 mg (0.09 mmol) **21** in 3 ml THF is added 12 mg (0.28 mmol) LiCl, 3.5 mg (0.0028 mmol) palladium(0)-tetrakis-(triphenylphosphine), and 0.027 ml (0.09 mmol) tributylvinyl stannane in 2 ml of benzene. The mixture is refluxed for 1 h, cooled to room temperature and 10 ml of a saturated solution of NaF is added. The reaction mixture is stirred for 1 h, extracted twice with petroleum ether, washed with brine, and dried over $MgSO_4$. The solvent is removed under reduced pressure, and the crude product is flash chromatographed with PE to yield 15 mg (0.073 mmol; 80%) of pure product **5**.
General Data: $C_{15}H_{24}$, MW = 204.36, R_f = 0.80 (PE).

^{1}H-NMR ($CDCl_3$): δ = 0.76 (s, 3H, H-11), 0.82 (d, 3H, H-13, J = 6.91 Hz), 0.92 (s, 3H, H-12), 0.95 (d, 3H, H-10, J = 7.20 Hz), 1.34-1.41 (m, 2H), 1.57-1.62 (m, 2H), 1.71-1.77 (m, 1H), 1.85 (d, 1H, J = 17.12 Hz), 1.97 (dd, 1H, J = 17.18 Hz, J = 6.63 Hz), 2.31 (q, 1H, H-9, J = 7.61 Hz), 4.89 (d, 1H, H-15, J = 10.79 Hz), 5.12 (d, 1H, H-15, J = 17.53 Hz), 5.70 (dd, 1H, H-7, J = 6.55 Hz, J = 3.10 Hz), 6.32 (dd, 1H, H-14, J = 17.41 Hz, J = 10.76 Hz).

^{13}C-NMR ($CDCl_3$): δ = 142.85 (s, C-8), 138.92 (d, C-14), 125.94 (d, C-7), 110.16 (t, C-15), 47.15 (s, C-1), 44.09 (s, C-5), 43.17 (d, C-9), 39.61 (t, C-6), 38.14 (d, C-4), 35.30, 30.32 (t, C-2, C-3), 20.84 (q, C-12), 20.60 (q, C-13), 14.29 (q, C-11), 13.52 (q, C-10).
MS (EI, 70 eV): m/z (%) = 204 (10) [M^+], 189 (4), 175 (2), 161 (3), 147 (3), 133 (5), 123 (14), 110 (57), 95 (100), 91 (11), 79 (17), 67 (8), 55 (9).

IR (Film): ν = 2959 (vs), 2927 (vs), 2872 (s), 2856 (s), 1733 (m), 1641 (m), 1461 (m), 1377 (m), 1357 (m), 1274 (m), 1212 (m), 1144 (m), 1124 (m), 1005 (m), 989 (m), 891 (m), 689 (m), 651 (m).

1,4,5,9-Tetramethyl-8-vinyl-bicyclo[4.3.0]nonane-8-ol [(±)-Pinguisenol] 6

To solution of 35 mg (0.18 mmol) **20** in 5 ml THF is added at 0 °C 0.29 ml (0.29 mmol) of a 1 M solution of vinylmagnesium bromide in THF. The mixture is stirred for an additional h at the same temperature, and is quenched with a saturated solution of NH_4Cl. The mixture is extracted twice with 20 ml ether, washed with brine, and dried over $MgSO_4$. The solvent is removed under reduced pressure and the crude product is flash chromatographed with EE/PE (3:7) to yield 35 mg (0.157mmol; 87%) of pure product **6**.
General Data: $C_{15}H_{26}O$, MW = 222.37, R_f = 0.81 (EE/PE 3:7).

^{1}H-NMR ($CDCl_3$):δ = 0.68 (s, 3H, H-11), 0.81 (d, 3H, H-13, J = 6.10 Hz), 0.83 (d, 3H, H-10, J = 6.03 Hz), 0.95 (s, 3H, H-12), 1.22-1.33 (m, 3H), 1.53 (q, 1H, H-9, J = 7.0 Hz), 1.59-1.75 (m, 3H), 1.77-1.82 (m, 2H), 2.32-2.40 (m, 1H), 5.00 (dd, 1H, H-15, J = 10.80 Hz, J = 1.43 Hz), 5.17 (dd, 1H, H-15, J = 17.23 Hz, J = 1.44 Hz), 5.79 (dd, 1H, H-14, J = 17.23 Hz, J = 10.75 Hz).

^{13}C-NMR ($CDCl_3$):δ = 147.63 (d, C-14), 110.63 (t, C-15), 75.63 (s, C-8), 47.34 (s, C-1), 45.14 (s, C-5), 40.27 (d, C-9), 36.19 (t, C-7), 34.90 (d, C-4), 33.85, 29.13, 25.96 (C-2, C-3, C-6), 19.21 (q, C-12), 17.84 (q, C-13), 14.59 (q, C-11), 10.06 (q, C-10).
MS (EI, 70 eV): m/z (%) = 204 (0.3) [M^+ -H_2O], 194 (5), 179 (8), 161 (4), 147 (3), 137 (20), 123 (14), 109 (28), 95 (10), 84 (56), 70 (24), 55(10), 43 (100).

IR (Film): ν = 3357 (br), 3347 (br), 3087 (s), 2962 (s), 2941 (s), 2931 (s), 2873 (s), 1711 (w), 1452 (m), 1380 (s), 1323 (m), 1294 (m), 1213 (m), 1126 (s), 1097 (s), 1047 (s), 995 (m), 917 (m), 800 (m), 735 (m), 668 (m), 646 (m).

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