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SYNTHESIS OF TRICYCLIC ANALOGUES OF ILLUDIN M

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Abstract: Tricyclic analogues of the cytotoxic sesquiterpene illudin M were synthesized from β-tetralone.

The illudins comprise a class of cytotoxic sesquiterpenes produced by the fungus *Omphalotus illudens*.[1-4] Illudins M (**1a**) and S (**1b**) were reported to be preferentially cytotoxic *in vitro* to a variety of human tumor cell lines. Selective toxicity was attributed to rapid uptake of the illudins by cells in an energy dependent process.[5] Once inside tumor cells, illudins are activated metabolically to a reactive intermediate that binds to DNA.[6-8] Although **1a** and **1b** lack an *in vivo* therapeutic window, the semisynthetic illudin derivatives dehydroilludin M (**2**) and acylfulvene (**3**) possess greatly improved *in vivo* efficacy against a number of adenocarcinomas.[9]

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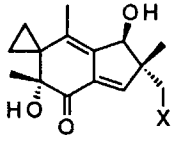
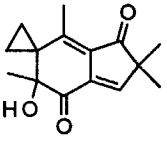


1a X = H
1b X = OH



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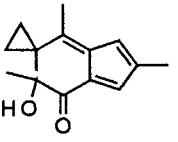
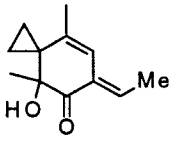


3

Initial SAR efforts on semisynthetic illudin analogues have shown that the spirocyclopropane and unsaturated ketone constitute a bis-electrophile that is essential for antitumor activity.[6] A subsequent SAR study on totally synthetic bicyclic illudin analogues demonstrated that the fused cyclopentane ring is not required for antitumor activity.[10] In fact, bicyclic illudin analogue **4** is more potent than **1a** or **2** against human tumor cells of epithelial origin *in vitro*. As part of our illudin analogue SAR program, tricyclic benz-fused analogues **5-7** were synthesized. Although these new analogues depart significantly in structure from the native illudins, compounds **5-7** preserve the core substructure that constitutes the putative illudin pharmacophore. Herein, the synthesis of **5-7** is described.



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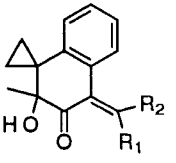
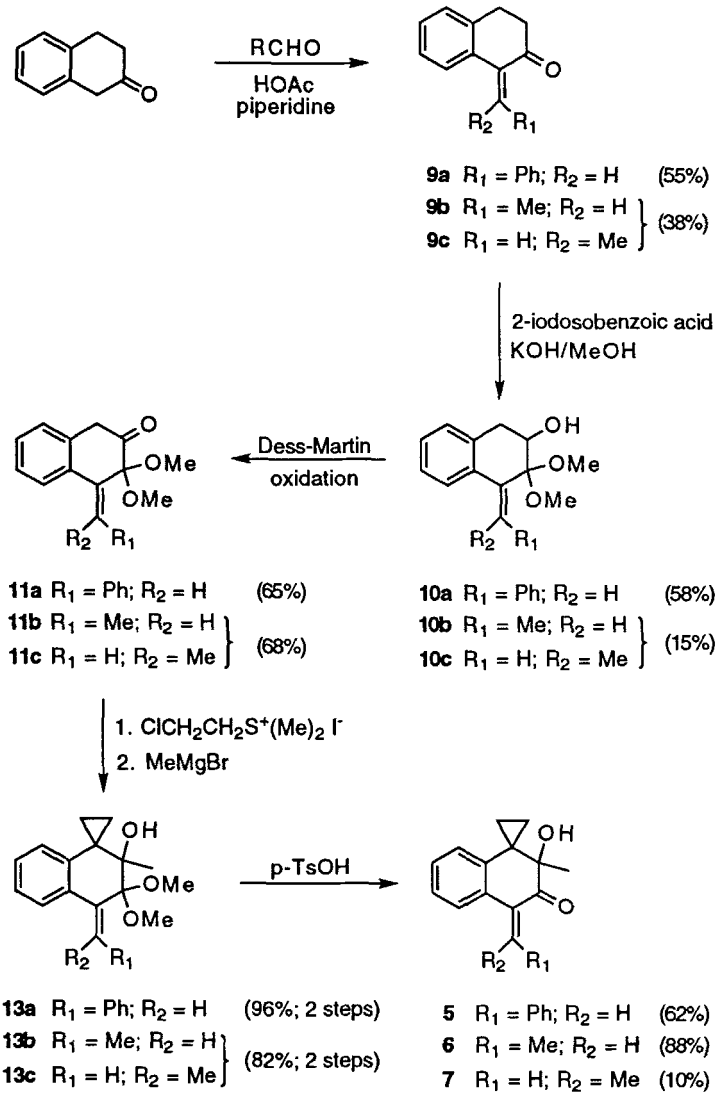


5 R_1 = Ph; R_2 = H
6 R_1 = Me; R_2 = H
7 R_1 = H; R_2 = Me

The synthesis of **5-7** is outlined in Scheme 1. Condensation of β-tetralone with benzaldehyde or acetaldehyde gave enones **9a-c**. The

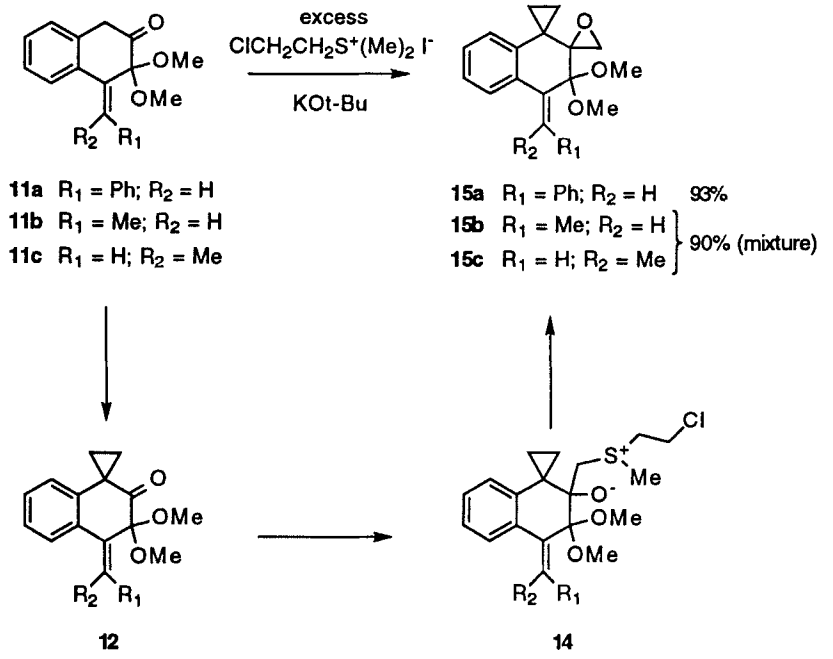
Scheme 1.



benzaldehyde condensation product **9a** formed exclusively in the Z-configuration, whereas the acetaldehyde condensation product was an inseparable mixture of double-bond isomers **9b** and **9c**. Enones **9a-c** were converted to α-hydroxy dimethyl acetals **10a-c** via treatment with iodosobenzoic acid and methanolic KOH.[11] This step was key to the synthesis in that it provided a means to distinguish between two adjacent oxidized carbons through the generation of a protected ketol. The secondary alcohols were then oxidized with the Dess-Martin reagent to give α-keto ketals **11a-c**.[12] The spirocyclopropane group was introduced via *t*-butoxide-mediated dialkylation of chloroethyldimethylsulfonium iodide.[13] The success of this reaction depends on maintaining a 1:1 stoichiometry of reagents. If excess chloroethyldimethylsulfonium iodide is used, then spiroepoxide **14** is produced exclusively. The probable mechanism of this reaction is shown in Scheme 2. After the spirocyclopropanation step, the nonenolizable ketone **12** is more susceptible to nucleophilic attack by the sulfur ylid that is generated by proton abstraction of the sulfonium iodide.[14] The final two steps required to produce illudin analogues **5-7** were (1) methylation of the ketone with MeMgBr to give tertiary alcohols **13**, then (2) acid-mediated deprotection of the dimethyl ketal. The isomers **6** and **7** were separated by chromatography.

In summary, a short series of a new class of illudin analogues has been synthesized. The synthesis utilized an oxidation-ketalization reaction that allowed for polyfunctionalization of the β-tetralone ring by protection of the electrophilic enone. The biological activity of these compounds will be reported elsewhere.

Scheme 2.



Experimental Section

General. Mass spectra were determined at an ionizing voltage of 70 eV. ^{1}H and ^{13}C NMR spectra were measured at 300 and 75 MHz. All chromatography columns used Merck silica gel 60 (230-400 mesh) unless specified otherwise.

Preparation of 5. To a stirred solution of **13a** (320 mg, 1.0 mmol) and acetone (35 mL) was added *p*-toluenesulfonic acid (20 mg) at 25 °C. The reaction was heated to 40 °C with stirring for 30 min, then concentrated to a solid. The solid was chromatographed (35% ethyl acetate-hexane) to give 290 mg of a yellow solid which was

recrystallized (hexane) to give 180 mg (62%) of **5** as a light yellow solid: mp 139-142 °C; IR (KBr) 3600-3400, 1688, 1479, 1229, 1128, 1068 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.50 - 6.90 (m, 10H), 3.62 (s, 1H), 1.40 - 1.22 (m, 1H), 1.20 - 1.15 (m, 2H), 1.12 (s, 3H), 0.60 - 0.46 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 203.2, 140.6, 139.3, 135.5, 132.3, 130.2, 129.6, 129.3, 128.8, 128.7, 128.6, 125.9, 124.5, 73.8, 28.2, 24.5, 12.3, 4.1. Anal. Calcd for $C_{20}H_{18}O_3$: C, 82.73; H, 6.25. Found: C, 82.34, H, 6.26.

Preparation of 6 and 7. **6** and **7** were prepared as a mixture in a similar manner to that used for **5** from a mixture of **13b** and **c**. Chromatographic separation (10% ethyl acetate - hexane) afforded 310 mg (88%) of **6** as a white solid and 35 mg (10%) of **7** as a pale yellow gum. Compound **6**: mp 25 - 27 °C; IR (KBr) 3600 - 3400, 1694, 1606, 1482, 1230, 1142, 1101 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.52 - 7.44 (m, 1H), 7.35 (q, J = 7.4 Hz, 1H), 7.30 - 7.20 (m, 2H), 7.17 - 7.05 (m, 1H), 3.63 (s, 1H), 2.20 (d, J = 7.4 Hz, 3H), 1.40 - 1.25 (m, 1H), 1.20 - 1.05 (m, 2H), 1.12 (s, 3H), 0.40 - 0.30 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 202.3, 140.1, 139.6, 132.8, 132.1, 128.2, 128.0, 126.1, 124.2, 73.4, 28.0, 24.3, 16.5, 12.4, 4.1; Anal. Calcd for $C_{15}H_{16}O_2$: C, 78.92; H, 7.06. Found: C, 78.70; H, 7.11. Compound **7**: IR (KBr) 3600 - 3400, 1695, 1606, 1482, 1363, 1230, 1140, 1101 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.60 - 7.52 (m, 1H), 7.30 - 7.20 (m, 2H), 7.02 - 6.92 (m, 2H), 3.92 (s, 1H), 2.35 (s, 3H), 1.38 - 1.28 (m, 1H), 1.23 (s, 3H), 1.20 - 1.05 (m, 2H), 0.40 - 0.30 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 203.0, 139.7, 138.3, 134.6, 131.3, 128.1, 126.5, 123.3, 123.0, 74.4, 28.8, 23.6, 16.8, 13.9, 5.2; Anal. Calcd for $C_{15}H_{16}O_2$: C, 78.92; H, 7.06. Found: C, 78.69; H, 7.26.

Preparation of 13a. To a stirred solution of β-tetralone (29 g, 200 mmol), acetic acid (1 mL), piperidine (2 mL), and toluene (100 mL) was added benzaldehyde (21 g, 200 mmol). The reaction was stirred at reflux for 4 h. Water (3 - 4 mL) was removed via a Dean-Stark trap. The reaction mixture was cooled to 25 °C and washed successively with saturated $NaHCO_3$ solution (200 mL), 5% aqueous HCl (200 mL), and brine (200 mL). The organic layer was dried (Na_2SO_4) and concentrated to afford a yellow solid that was recrystallized (toluene - hexane) to give 25 g (55%) of **9a** as light yellow crystals: mp 88 - 92 °C; IR (KBr) 1689, 1595, 1244, 1182, 771 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.68 (s, 1H), 7.50 - 7.00 (m, 9H), 3.10 (t, J = 7 Hz, 2H), 2.64 (t, J = 7 Hz, 2H); CI-MS 235 (M + 1).

To a stirred solution of 2-iodosobenzoic acid (5.0 g, 19 mmol), KOH (2.5 g, 44 mmol), and MeOH (50 mL) was added **9a** (3.1 g, 15 mmol) at 0 °C. The resulting suspension was stirred at this temperature for 2 h, then warmed to 25 °C and stirred for 12 h. The reaction mixture became a brown solution which was concentrated, and partitioned between CH_2Cl_2 and H_2O. The organic extract was dried (Na_2SO_4), concentrated, then chromatographed (neutral alumina eluted with 20 % ethyl acetate - hexane) to give 2.5 g (58%) of **10a** as a white solid: IR (KBr) 2914, 1446, 1265, 1077, 1058, 1010, 932 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.23 - 7.10 (m, 9H), 6.9 - 6.8 (m, 1H), 4.35 (dd, J = 5.2 and 1.2 Hz, 1H), 3.41 (s, 3H), 3.24 (dd, J = 17 and 5.2 Hz), 3.12 (s, 3H), 3.11 (s, 1H), 3.09 (dd, J = 17 and 5.2 Hz, 1H); CI-MS 297 (M + 1).

A solution that consisted of **10a** (5.1 g, 17 mmol), Dess-Martin reagent[12] (11 g, 25 mmol), and CH_2Cl_2 (100 mL) was stirred at 25 °C for 48h. *2N* NaOH (100 mL) was added to the reaction mixture which was then extracted with ether (2 x 400 mL). The organic layers were combined

and washed with brine (200 mL), dried (Na_2SO_4), and concentrated to a light brown oil. This oil was chromatographed (20% ethyl acetate - hexane) to give 3.3 g (65%) of **11a** as a pale yellow oil: IR (KBr) 2950, 2805, 1702, 1194, 1136, 1034 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.22 - 7.10 (m, 9H), 7.00 - 7.92 (m, 1H), 3.85 (s, 2H), 3.36 (s, 3H), 3.35 (s, 3H); CI-MS 312 ($M + NH_4^+$).

To a stirred solution of **11a** (2.1 g, 7.1 mmol) and 1*M* potassium *t*-butoxide/*t*-butanol (30 mL) was added chloroethyldimethylsulfonium iodide (2.2 g, 8.6 mmol) at 25 °C under N_2. The reaction was stirred for 2h, then saturated $NaHCO_3$ solution (50 mL) was added. The mixture was extracted with CH_2Cl_2 (3 x 200 mL), dried (Na_2SO_4), and concentrated to give a brown oil. This oil was chromatographed (30% ethyl acetate - hexane) to give 1.6 g (70%) of **12a** as a pale yellow solid: IR (KBr) 3010, 2922, 1719, 1214, 1058, 1006 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.22 - 7.16 (m, 8H), 6.90 (m, 1H), 6.74 (d, J = 7.9 Hz, 1H), 3.40 (s, 6H), 1.84 - 1.80 (m, 2H), 1.44 - 1.41 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 202.8, 138.4, 136.3, 133.7, 133.1, 132.0, 129.5, 129.0, 128.4, 128.1, 127.6, 125.1, 121.0, 100.2, 51.1, 30.5, 24.1; CI-MS 321 (M + 1).

MeMgBr (1.2 mL, 1.4 *M* in ether) was added slowly to a stirred solution of **12a** (350 mg, 1.1 mmol) and THF (10 mL) at -78 °C under N_2. The reaction was allowed to warm to 25 °C, then stirred for 10 min. Saturated $NaHCO_3$ solution (10 mL) was added, then extracted with ethyl acetate (2 x 10 mL). The combined organic layers were washed with brine (10 mL), dried (Na_2SO_4), and concentrated to give 340 mg (96%) of **13a** as a light yellow solid: mp 106 - 108 °C; IR (KBr) 3600 - 3200, 1129, 1084, 1058, 1041 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.22 - 7.15 (m, 7H), 7.15 - 7.04 (m, 1H), 6.78 (t, J = 7.2 Hz, 1H), 6.65 (d, J = 8 Hz, 1H), 3.64 (s, 3H), 3.18 (s,

3H), 2.10 (s, 1H), 1.50 - 1.40 (m, 1H), 1.28 (s, 3H), 1.18 - 1.05 (m, 2H), 0.70 - 0.60 (m, 1H); Anal. Calcd for $C_{22}H_{24}O_3$: C, 78.54; H, 7.19. Found: C, 78.36; H, 7.32.

Preparation of 13b and c. **13b** and **c** were prepared as a mixture of E and Z isomers in a similar manner to that used for **13a** from β-tetralone in 20% yield (5 steps): mp 79 - 84 °C; IR (KBr) 3700 - 3300, 2939, 1138, 1097, 1062, 959 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.4 - 7.1 (m, 3H), 6.68 (d, J = 8 Hz, 1H), 6.38 (q, J = 7 Hz, 1H), 3.58 (s, 3H), 3.08 (s, 3H), 2.1 (s, 1H), 2.01 (d, J = 7 Hz, 3H), 1.50 - 1.40 (m, 1H), 1.15 (s, 3H), 1.08 - 1.00 (m, 2H), 0.68 - 0.55 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 141.9, 134.8, 132.4, 128.5, 127.4, 125.7, 124.0, 121.9, 101.1, 76.5, 51.7, 50.7, 29.8, 19.6, 15.7, 12.1; Anal. Calcd for $C_{17}H_{22}O_3$: C, 74.42; H, 8.08. Found: C, 74.32; H, 8.07.

Preparation of 15a. To a stirred solution of **11a** (1.8 g, 6.1 mmol) and 1*M* potassium *t*-butoxide/*t*-butanol (30 mL) was added chloroethyldimethylsulfonium iodide (2.2 g, 8.6 mmol) at 25 °C under N_2. The reaction was stirred for 2h, then saturated $NaHCO_3$ solution (50 mL) was added. The mixture was extracted with CH_2Cl_2 (3 x 200 mL), dried (Na_2SO_4), and concentrated to give a brown oil. This oil was chromatographed (25% ethyl acetate - hexane) to give a solid which was recrystallized (ethyl acetate - hexane) to give 1.9 g (93%) of **15a** as a light yellow solid: mp 139 - 142 °C; IR (KBr) 3061, 2990, 1602, 1482, 1211, 1080, 1056 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.40 - 7.10 (m, 7H), 7.02 (s, 1H), 6.83 (t, J = 7 Hz, 1H), 6.67 (d, J = 7 Hz, 1H), 3.53 (s, 3H), 3.17 (s, 3H), 2.84 (d, J = 6 Hz, 1H), 2.57 (d, J = 6 Hz, 1H), 1.48 - 1.30 (m, 1H), 1.05 - 0.90 (m, 1H), 0.90 - 0.70 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 142.2, 137.3,

136.7, 132.4, 129.6, 129.4, 128.1, 128.0, 127.0, 126.9, 124.3, 121.6, 98.6, 63.4, 51.6, 50.9, 50.3, 22.6, 19.0, 10.8; Anal. Calcd for $C_{22}H_{22}O_3$: C, 79.02; H, 6.63. Found: C, 78.87; H, 6.77.

Preparation of 15b and c. **15b** and **c** were prepared as a mixture of E and Z isomers in a similar manner to that used for **15a** in 90% yield: mp 92 - 96 °C; IR (KBr) 2939, 1232, 1184, 1147, 1084, 1066, 1040 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.40 - 7.30 (m, 1H), 7.20 - 7.08 (m, 2H, 6.70 - 6.60 (m, 1H), 6.18 (m, 1H), 3.45 (s, 3H), 3.13 (s, 3H), 2.80 (m, 1H), 2.46 (m, 1H), 1.38 - 1.25 (m, 1H), 1.20 - 1.05 (m, 2H), 1.96 (m, 3H), 0.42 - 0.32 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 141.7, 136.0, 133.3, 128.6, 127.3, 124.4, 123.5, 121.5, 98.7, 51.3, 50.8, 50.0, 27.6, 22.6, 19.0, 15.2, 11.3; Anal. Calcd for $C_{17}H_{20}O_3$: C, 74.97; H, 7.40. Found: C, 74.92; H, 7.41.

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