Total Synthesis of (±)-Illudin M

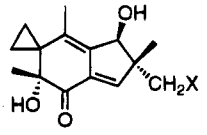
Frederick R. Kinder, Jr.,* and Kenneth W. Bair

Oncology Research Program, Preclinical Research, Sandoz Research Institute, Sandoz Pharmaceuticals Corporation, 59 Route 10, East Hanover, New Jersey 07936-1080

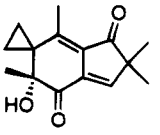
Received July 13, 1994®

(±)-Illudin M (**1**) was synthesized in six steps starting from 1-acetyl-1-(diazoacetyl)cyclopropane (**4**) and 4-bromo-5,5-dimethyl-2-cyclopentenone (**5**). The key step of the synthesis featured a carbonyl ylide 1,3-dipolar cycloaddition reaction that was mediated by the formation of a rhodium(II) carbenoid from **4** and catalytic rhodium(II) diacetate.

Illudin M (**1**) and S (**2**) are sesquiterpenes produced by the fungus *Omphalotus illudens*. The toxic properties of these compounds have been well documented over the last 40 years.[1-4] Kelner, McMorris, and Taetle have recently reported that the illudins demonstrated *in vitro* selective toxicity for tumor cells compared to normal cells.[5] They speculated the existence of an active transport pump in certain tumor cells not present in normal cells. After a prolonged exposure (>2 d), the illudins were toxic to a wide range of tumor cells and normal cells (several fibroblast cell lines). Under a shorter exposure (2 h), however, the illudins were selectively toxic for human myelocytic and epidermoid, lung, ovarian, and breast carcinoma cells from various species. Furthermore, the oxidized analog of illudin M **3** was shown to be less toxic to mice than illudin M.[6] The mechanism of



1 Illudin M X = H
2 Illudin S X=OH

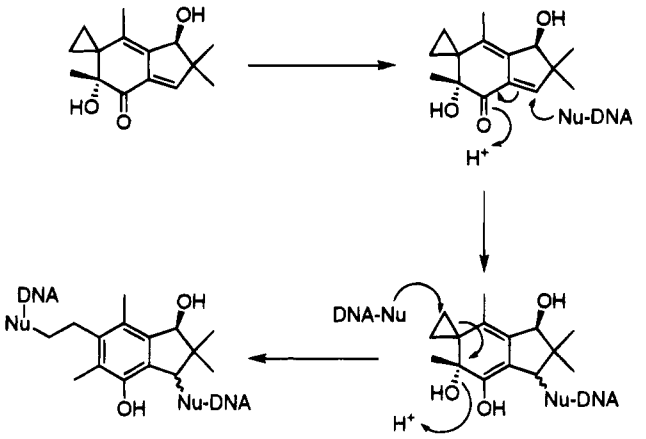


3 Dehydroilludin M

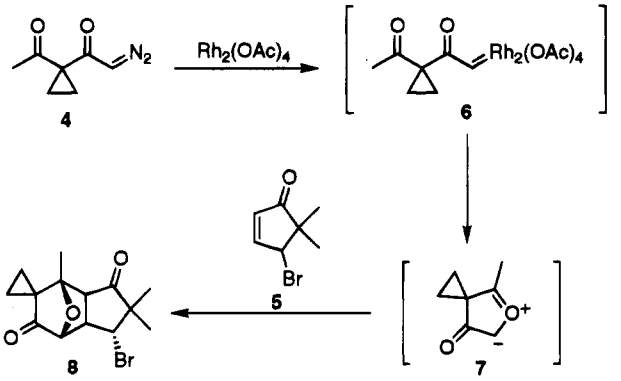
action for the illudins has been proposed as an acid catalyzed dialkylation of DNA (Scheme 1). Although cytokinetic experiments with HL60 cells have shown that illudin S primarily affects DNA synthesis, binding of illudin M or S to DNA has not been demonstrated.[6,7]

To date only one total synthesis of illudin M has been reported.[8] The synthesis is long (15 steps), and not amenable to modification for the preparation of illudin analogs. All analogs of the illudins reported thus far are derived from the natural products.[9,10]

Scheme 1



Scheme 2



In this paper we report a six-step total synthesis of (±)-illudin M from diazo ketone **4** and bromocyclopentenone **5**. Compound **4** was prepared in two steps from ethyl acetoacetate by a variation on the method reported by Padwa.[11] Compound **5** was prepared by the method of Matsumoto in two steps from 2,2-dimethylcyclopentanone.[12] The first and key step of the synthesis was a carbonyl ylide 1,3-dipolar cycloaddition reaction (Scheme 2). Formation of the ylide **7** occurs when **4** is treated with catalytic rhodium(II) diacetate dimer which generates a rhodium(II) carbenoid **6**.[11] This transient intermediate cyclizes via attack by the ketone oxygen five atoms away. The carbonyl ylide then undergoes a 1,3-dipolar cycloaddition reaction with the dipolarophile **5** to form the

® Abstract published in *Advance ACS Abstracts,* October 15, 1994.

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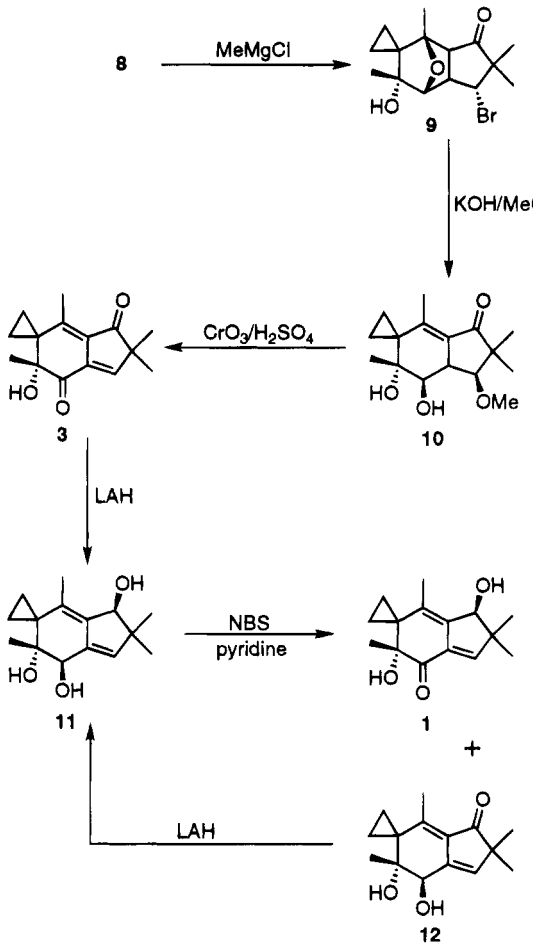
0022-3263/94/1959-6965$04.50/0

Scheme 3



carbon skeleton of illudin M **8** as a single diastereomer in 40–50% yield.

We have found that the cycloaddition reaction proceeded best when the dipole precursor was added slowly to a dichloromethane solution of the catalyst and dipolarophile heated at reflux. The presence of catalytic amounts of DMF improved the yield further. Yields of 5–10% were observed when rhodium(II) diacetate dimer was simply added to a dichloromethane solution of **4** and **5** irrespective of temperature. We believe that the DMF binds reversibly to the rhodium(II) diacetate resulting in slower carbenoid formation. The decreased carbenoid concentration limits competing side reactions such as dimerization.

Several functional group manipulations remained in order to complete the synthesis of **1** (Scheme 3). Compound **8** was regio- and stereospecifically methylated with methylmagnesium chloride to give the tertiary alcohol **9** which was not isolated but subsequently treated with methanolic KOH. This not only induced β-elimination of the bridgehead ether linkage, but also displaced the neopentyl bromide with a methoxy moiety to give **10** in 42% yield.[13]

Oxidation of **10** and subsequent acid-catalyzed elimination of methanol by using the Jones reagent produced dehydroilludin M (**3**) in 54% yield. This reaction did not occur using other oxidation methodologies. For example the Swern reaction (or its variations) and PCC gave complex product mixtures. No reaction was observed when **10** was treated with NBS–pyridine.

The final transformation of **3** to illudin M was stereoselective reduction of the five-ring ketone to the secondary alcohol. Attempted selective reduction of **3** with 1 equiv of DIBALH gave only the undesired secondary alcohol isomer **12**. Treatment of **3** with excess LAH gave the known triol **11** in 74% yield.[9] Although **11** has been converted to the final product **1** using a four-step sequence,[9] we found that NBS–pyridine gave illudin M in 30% yield as well as isomer **12** in 23% yield. Both of these compounds were separable with column chromatography and **12** could be easily recycled back to triol **11**.

In conclusion, we have demonstrated the application of carbonyl ylide cycloaddition methodology toward the total synthesis of (±)-illudin M. This synthesis not only improved upon the length of the only other reported synthesis, but makes the preparation of analogs of illudin M possible through altering the dipole or dipolarophile in the cycloaddition step.

Experimental Section

General. Melting points are uncorrected. Mass spectra were determined at an ionizing voltage of 70 eV. ^1H and ^{13}C NMR spectra were measured at 300 and 75 MHz. All chromatography columns used Merck silica gel 60 (230–400 mesh). Ethereal solutions of diazomethane were prepared from the reaction of Diazald with KOH and used immediately.

1-Acetyl-1-(diazoacetyl)cyclopropane (4). To a stirred suspension of acetylcyclopropane-1-carboxylic acid[14] (15 g, 120 mmol), K_2CO_3 (65 g, 470 mmol), and CH_2Cl_2 (250 mL) was added methyl chloroformate (23 mL, 290 mmol) at 5 °C. The mixture was stirred for 2 h, suction-filtered through a pad of silica gel, and then concentrated to an oil. The crude mixed anhydride was redissolved in 190 mL of CH_2Cl_2 and added rapidly dropwise to ethereal diazomethane solution (300 mmol). The reaction was stirred at 25 °C for 16 h, concentrated to a deep yellow oil, and then chromatographed (40% ethyl acetate–hexanes) to give 14.3 g (80%) of **4**[11] as a yellow oil: IR (neat) 3135, 3096, 3009, 2188, 2107, 1689, 1622, 1416, 1282, 1156 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.45 (m, 2H), 1.61 (m, 2H), 2.14 (s, 3H), 5.96 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 203.5, 189.7, 56.8, 40.6, 26.7, 17.8. Anal. Calcd for $C_7H_8N_2O_2$: C, 55.26; H, 5.30. Found: C, 55.57; H, 5.45.

1-Bromo-1′,3a′,4′,7a′-tetrahydro-2′,2′,4′-trimethylspiro-[cyclopropane-1,5′-[5*H*]-[4,7]epoxyindene]-3′,6′(2′*H*,7′*H*)-dione (8). To a stirred solution of 4-bromo-5,5-dimethyl-2-cyclopentenone (**5**)[12] (6.0 g, 32 mmol), Rh_2OAc_4 (150 mg), DMF (0.5 mL), and CH_2Cl_2 (50 mL) was added a solution of **4** (6.0 g, 40 mmol) and CH_2Cl_2 (50 mL) dropwise (about 3 drops/s) at reflux. The reaction was stirred at reflux for 30 min following addition and then concentrated to a dark oil. The crude cycloaddition product was purified by chromatography (15% ethyl acetate–hexanes) to give 4.8 g (49%) of **8** as a pale yellow solid: mp 141–142 °C; IR (KBr) 2973, 2934, 1758, 1746, 1460, 1257, 1235 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.70 (m, 1H), 1.05 (m, 1H), 1.08 (s, 3H), 1.12 (s, 3H), 1.18 (m, 2H), 1.37 (s, 3H), 1.4 (m, 1H), 2.85 (d, J = 7.5 Hz, 1H), 3.15 (t, J = 7.5 Hz, 1H), 3.95 (d, J = 7.5 Hz, 1H), 4.48 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 212.1, 210.8, 87.6, 82.5, 58.2, 56.4, 52.4, 50.1, 39.8, 22.4, 19.6, 14.8, 13.7, 11.9. Anal. Calcd for $C_{14}H_{17}BrO_3$: C, 53.69; H, 5.47; Br, 25.51. Found: C, 53.71; H, 5.47; Br, 25.60.

1′,6′,7′,7a′-tetrahydro-6′,7′-dihydroxy-1′-methoxy-2′,2′,4′,6′-tetramethylspiro[cyclopropane-1,5′-[5*H*]inden]-3′(2′*H*)-one (10). Methylmagnesium chloride (21 mL, 62 mmol, 3.0 M in THF) was added dropwise to a stirred solution of **8** (4.8 g, 15 mmol) and THF (150 mL) at −78 °C under N_2.

(13) While this manuscript was in preparation, Padwa and coworkers reported that the rhodium(II)-catalyzed cycloaddition products of **4** and cyclopentenone and dimethyl maleate undergo bridgehead ether cleavage with samarium iodide and LDA respectively, see Padwa, A.; Sandanayaka, V. P.; Curtis, E. A. *J. Am. Chem. Soc.* **1994**, *116*, 2667.

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The mixture was stirred at this temperature for 1 h and then at 5 °C for 2 h. The reaction was quenched with methanol (50 mL), concentrated to a thick oil, and then redissolved in a 10% KOH–methanol solution (150 mL). The mixture was stirred at reflux for 3 h, cooled to room temperature, and partitioned between CH_2Cl_2 and water. The combined organic layers were dried (Na_2SO_4) and concentrated to an oil that was chromatographed (gradient of 50% ethyl acetate–hexane to 100% ethyl acetate) to give 1.8 g (42%) of **10** as a white solid: mp 207–208 °C; IR (KBr) 3410, 3030, 2932, 2871, 1735, 1677, 1598, 1372, 1261, 1195 cm^{-1}; ^1H NMR ($CDCl_3$ and CD_3OD) δ 0.93–1.15 (m, 4H), 0.95 (s, 3H), 1.05 (s, 3H), 1.13 (s, 3H) 1.80 (d, J = 3.7 Hz, 3H), 2.93 (br s, 2H), 3.10 (dt, J = 10 Hz,3.7Hz, 1H), 3.48 (s, 3H), 3.58 (d, J = 10 Hz, 1H), 3.77 (d, J = 3.7 Hz, 1H); ^{13}C NMR ($CDCl_3$ and CD_3OD) δ 208.9, 154.7, 127.1, 86.2, 74.5, 72.5, 60.8, 44.4, 30.2, 24.8, 23.9, 19.9, 15.3, 14.1. Anal. Calcd for $C_{16}H_{24}O_4$: C, 68.55; H, 8.63. Found: C, 68.46; H, 8.54.

Dehydroilludin M (3). A solution consisting of CrO_3 (2.4 g, 24 mmol), concd H_2SO_4 (2.4 mL), and water (10 mL) was added portionwise to a stirred solution of **10** (1.7 g, 6.1 mmol) and acetone (100 mL) at 5 °C, stirred for 13 min, and then quenched with 2-propanol (100 mL). The mixture was stirred at room temperature for 1 h and then suction-filtered through a pad of silica gel. The filtrate was concentrated and chromatographed (20% ethyl acetate–hexanes) to give 0.8 g (54%) of **3** as a white solid:[6,9] mp 66–67 °C; IR (KBr) 3487, 2968, 2928, 2866, 1704, 1617, 1598, 1463, 1259, 1242, 1165 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.60 (m, 1H), 1.05 (m, 1H), 1.18 (m, 1H), 1.20 (s, 3H), 1.24 (s, 3H), 1.33 (m, 1H), 1.34 (s, 3H), 2.05 (s, 3H), 3.61 (s, 1H), 6.83 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 206.7, 199.0, 151.3, 141.8, 134.8, 129.6, 75.6, 51.5, 33.9, 25.1, 22.94, 22.92, 12.9, 11.7. Anal. Calcd for $C_{15}H_{18}O_3 \cdot 0.4H_2O$: C, 71.07; H, 7.47. Found: C, 71.14; H, 7.58.

Dihydroilludin M (11). A solution of **3** (0.8 g, 3 mmol) and THF (30 mL) was added dropwise to a stirred suspension of LAH (0.4 g, 10 mmol) and THF (20 mL) at 5 °C under N_2. The reaction was stirred under these conditions for 1.5 h and then quenched with the sequential dropwise addition of the following: H_2O (0.4 mL), 15% NaOH solution (0.4 mL), and H_2O (1.2 mL). This mixture was stirred for 16 h at 25 °C and then suction-filtered through silica gel. The filtrate was concentrated to give 0.6 g (74%) of **11** as a white crystalline solid:[9] mp 152–153 °C; IR (KBr) 3421, 3009, 2953, 2863, 1650, 1632, 1359, 1248, 1112 cm^{-1}; ^1H NMR ($CDCl_3$ and CD_3OD) δ 0.39 (m, 1H), 0.68 (m, 1H), 0.81 (m, 1H), 0.93 (m, 1H), 0.94 (s, 3H), 1.06 (s, 6H), 1.53 (s, 3H), 3.90 (br s, 3H), 4.09 (s, 1H), 4.26 (s, 1H), 5.56 (s, 1H); ^{13}C NMR ($CDCl_3$ and CD_3OD) δ 140.5, 140.2, 135.7, 132.0, 75.0, 74.5, 50.5, 49.8, 49.1, 29.2, 23.4, 19.6, 14.3. Anal. Calcd for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86. Found: C,71.71; H, 8.72.

Illudin M (1). NBS (0.6 g, 3 mmol) was added in one portion to a stirred solution of **11** (0.8 g, 3 mmol), pyridine (0.8 mL, 10 mmol), and CH_2Cl_2 (250 mL) at 25 °C and then stirred for 1.5 h. The reaction was quenched with 2-propanol (40 mL), stirred for 1 h, and then concentrated to an oil. This oil was chromatographed (gradient of 20% ethyl acetate–hexane to 40% ethyl acetate–hexane) to give 0.24 g (30%) of **1** as a pale yellow gum:[15] IR (neat) 3444, 2968, 2929, 2691, 1695, 1592, 1447, 1265, 1106 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.43 (m, 1H), 0.83 (m, 1H), 0.96 (m, 1H), 1.11 (s, 3H), 1.15 (m, 1H), 1.17 (s, 3H), 1.37 (s, 3H), 1.55 (br s, 1H), 1.69 (s, 3H), 3.55 (br s, 1H), 4.41 (s, 1H), 6.54 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 200.5, 146.6, 138.8, 134.5, 132.9, 78.9, 75.9, 49.1, 31.6, 27.3, 24.8, 20.5, 14.2; HRMS calcd for $C_{15}H_{20}O_3$ 248.1412, found 248.1417.

In addition 0.18 g (23%) of the illudin M isomer **12** was isolated from the column as a white solid: 141–142 °C; IR (KBr) 3426, 3012, 2968, 2865, 1712, 1629, 1614, 1461, 1374, 1268, 1142 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.64 (m, 1H), 0.93 (m, 1H), 1.08 (s, 3H), 1.1 (s, 6H), 1.12 (m, 1H), 1.28 (m, 1H), 1.91 (s, 3H), 2.13 (br s, 1H), 2.55 (br s, 1H), 4.36 (s, 1H), 5.94 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 209.1, 148.7, 141.1, 130.1, 129.8, 74.1, 72.9, 50.1, 32.9, 24.3, 23.3, 19.5, 12.4, 11.4. Anal. Calcd for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12. Found: C, 72.36; H, 8.21.

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