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Chang-Joo Lee [a] , Bradford P. Mundy [a] & Jong-Gab Jun [b]

[a] Department of Chemistry , Montana State University , Bozeman, Montana, 59717

[b] Department of Chemistry , Hallym University , Chunchon, 200, Korea

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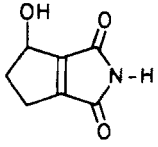
FORMAL SYNTHESIS OF MALEIMYCIN.

*Chang-Joo Lee and Bradford P. Mundy**
Department of Chemistry, Montana State University
Bozeman, Montana 59717

Jong-Gab Jun
Department of Chemistry, Hallym University
Chunchon 200, Korea

***ABSTRACT:** A formal synthesis of maleimycin is reported. A key feature includes formation of a tricyclic intermediate that undergoes flash vacuum thermolysis to afford the required skeletal framework of the target molecule.*

Maleimycin, **1**, an antibiotic isolated from the culture filtrate of Streptomyces showdoensis[1], shows activity against bacteria and is also active against leukemia L-1210 cells. Many N-substituted imides of general structure **2** are also known to have fungicidal and herbicidal activity[2]. Based on our early work on dianion-mediated reactions[3], we imagined the preparation of the requisite skeletal features for **1** and **2** in two to three steps. We report here a simple entry into these molecules.



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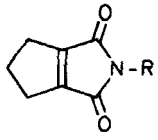

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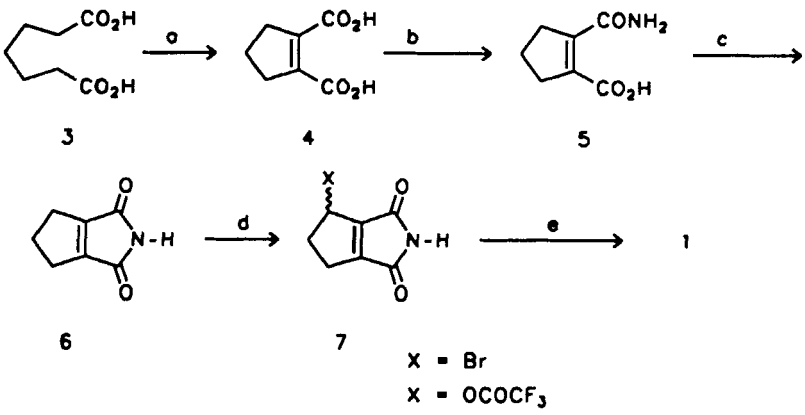
* *To whom correspondence should be addressed.*



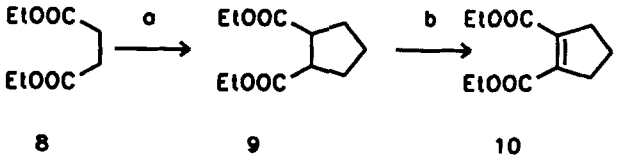
a. (1) $SOCl_2$, (2) Br_2, (3) MeOH, (4) NaH, DMF
b. Ac_2O, NH_4OH c. $(TFAc)_2O$ d. NBS, then TFAcOAg
e. pH = 4

Figure 1.

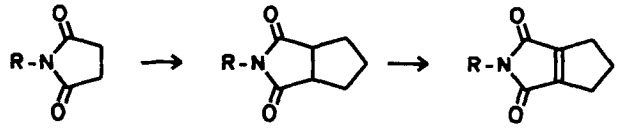
Maleimycin was prepared by Weinreb according to the steps outlined in Figure 1[4]. The intermediate, 6, reported in this prior work becomes the immediate target for our simplified entry.

Based on our conversions, such as **8** ---> **10** (**Equation 1**), we envisioned a strategy (**Equation 2**) for the simple synthesis. However, we could not, under any circumstances, place the needed unsaturation in the ring. We do not have a full appreciation for why there is so much difficulty in carrying out this transformation. Did we make the dianion? We answered this key question by readily converting **12** to **14** - **16**.

The synthesis required modification. Readily-available **17b** (from **17a**, 91%) was converted by dianion annulation to **18a** (61%). Deprotection with BBr_3 provided **18b** (83%). This molecule readily underwent retro-Diels Alder reaction under FVT conditions (~600°) to provide 60% **6**, and 35% starting material. Although the reaction scheme is not as simple as first

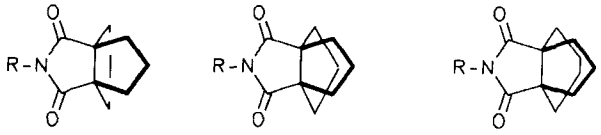


8 9 10 Eq. 1



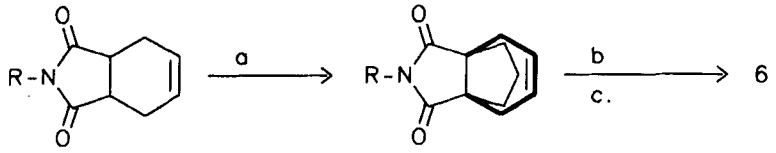
11 12 13 Eq. 2

a. LDA/ 1,3-dibromopropane
b. LDA then I_2



14 15 16

designed by **Equation 2**, it does provide the maleimycin precursor in four simple steps, including protection and deprotection, and establishes a general route to substituted maleimides as well as a formal synthesis of maleimycin.



a. LDA/ 1,3-dibromopropane b. BBr_3 c. Heat

17a R = H 18a R = CH_2-O-CH_2-Ph
17b R = CH_2-O-CH_2-Ph 18b R = H

Experimental:

N-Benzyloxymethyl-cis-1,2,3,6-tetrahydrophthalimide (17b):

A solution, prepared from cis-1,2,3,6-tetrahydrophthalimide (**17a**, 2.0 g, 0.013 mol), benzyl chloromethyl ether (2.2 mL, 0.016 mol), and K_2CO_3 (2.7 g, 0.02 mol), under argon atmosphere was refluxed overnight. After neutralization with dil HCl, the reaction mixture was extracted with dichloromethane. The combined extracts were washed with brine, dried over anhyd $MgSO_4$, filtered and reduced in volume by rotary evaporation. Flash chromatography (silica gel, 1:1 hexane/EtOAc) gave 2.6 g (91%) of the desired protected imide.

^{1}H-NMR ($CDCl_3$): 2.16-2.23 (2H,m); 2.53-2.60 (2H,m); 2.95-2.99 (2H,m); 4.53 (2H,s); 4.95 (2H,s); 5.86-5.88 (2H,m); 7.29 (5H,m)

^{13}C-NMR ($CDCl_3$): 23.36 (t); 39.08)d); 67.77 (t); 71.97 (t); 126.96 (d); 127.61 (d); 127.68 (d); 128.35 (d); 128.54 (d); 137.57 (s); 179.70 (s).

MS (EI) m/e (% abundance): 271 (m^+,3); 165 (100); 136 (4); 111 (10); 91 (36); 79 (25); 65 (7); 41 (2).

HRMS: Calculated for $C_{16}H_{17}O_3N$ 271.1208; found 271.1209.

N-Benzyloxymethyl-7,9-dioxo-8-azatricyclo[4.3.3.0]dodec-3-ene (18a):

A solution of 15 mL dry THF, 0.56 mL of 10M n-BuLi (0.0056 mol) and 0.83 mL of diisopropylamine (0.0059 mol) was stirred under argon at -78°C for 15 min. To this solution was slowly added 0.50 g of **17b** (0.0023 mol), resulting in a red-colored solution of the dianion. After 15 min, 1,3-dibromopropane (0.28 mL, 0.0028 mol) was added, dropwise. When the addition was completed the reaction mixture was allowed to warm to rt. After several more hours, the reaction mixture was neutralized with conc HCl. Salts were removed by filtration and excess solvent was removed from the filtrate by rotary evaporation. The residue was extracted with dichloromethane, and after drying the combined extracts over anhyd $MgSO_4$, excess solvent was removed by rotary evaporation. The crude

residue was subjected to flash chromatography (silica gel, 1:1, hexane/EtOAc) to give 0.36 g (61%) of **18a**.

^{1}H-NMR ($CDCl_3$): 1.21-2.70 (10H, m); 4.50 (2H,s); 4.92 (2H,s); 5.88-5.90 (2H,m); 7.29 (5H,m).

^{13}C-NMR ($CDCl_3$): 24.46 (t); 31.12 (t); 38.18 (t); 56.05 (s); 67.72 (t); 71.76 (t); 127.69 (d); 127.78 (d); 127.94 (d); 128.34 (d); 128.50 (d); 131.86 (d); 137.46 (s); 182.32 (s).

MS: (EI) m/e (% abundance): 311 (M^+); 205 (100); 176 (4); 148 (6); 119 (20); 91 (84); 65 (13); 41 (2).

HRMS: Calculated for $C_{19}H_{21}O_3N$, 311.1521; found 311.1529

7,9-Dioxo-8-azatricyclo[4.3.3.0]dodec-3-ene (18b):

A solution of **18a** (33 mg, 0.13 mmole), BBr_3 (0.15 mL, 0.16 mmole) and 5 mL benzene was stirred at rt for 1 hr. Methanol (0.2 mL) was added to the reaction mixture and after 30 min the low-boiling solvents were removed by rotary evaporation. The residue, in 4 mL water, was heated to boiling for 30 min. Water was removed by vacuum and the resulting solid was extracted with dichloromethane. The combined extracts were dried over anhyd $MgSO_4$, and after removal of solvent the crude product was chromatographed (silica gel, 1:1 hexane/EtOAc) to yield 20 mg (83%) of product.

^{1}H-NMR ($CDCl_3$): 1.33-2.68 (10H, m); 5.90-5.92 (2H,m); 8.85 (1H,br)

^{13}C-NMR ($CDCl_3$): 24.46 (t); 30.96 (t); 38.05 (t); 57.19 (s); 128.44 (d); 182.90 (s)

MS (EI) m/e (% abundance): 191 (M^+, 100); 148 (42); 120 (47); 91 (61); 65 (9); 41 (5)

HRMS: Calculated for $C_{11}H_{13}O_2N$, 191.0946; Found, 191.0938

2,4-Dioxo-3-azabicyclo[3.3.0]oct-$\Delta^{1,5}$-ene (6):

The propellane (**18b**, 20 mg, 0.11 mmol) was passed through a FVT apparatus at about 600°C under high vacuum. The products were collected in a trap cooled by dry ice, and consisted of 35% starting material, 60%

product and 5% of an unidentified material. The product was purified by flash chromatography (silica gel; dichloromethane, hexane, EtOAc, 20:1:1) to give a crystalline sample, mp 178-179° (lit[4], 177-179°).

^{1}H-NMR ($CDCl_3$): 2.43 (2H, pentet, J=7.3 Hz); 2.65 (4H, t, J=7.3 Hz); 7.05 (1H, br).

^{13}C-NMR ($CDCl_3$): 26.40 (t), 27.55 (t); 154.61 (s); 166.66 (s).

MS (EI) m/e (% abundance): 137 (M^+, 13); 94 (77); 66 (100); 52 (8); 41 (3).

HRMS: Calculated for $C_7H_7O_2N$, 137.0477; found, 137.0474

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References and Notes:

1. E.F. Elstner, D.M. Carnes, R.J. Suhadolnik, G.P. Kreishman, M.P. Schweizer ar R.K. Robins, **Biochemistry**, (1973), 12, 4992.

2. Representative of the patents from the Mitsubishi Chemical Industry is: Kasugai, M. Tomita, H. Ohta, T. Jikihara, and H. Watanabe, **Chemical Abstract** (1976), 84, 268625.

3. D. Wilkening and B.P. Mundy, **Synth. Commun**, (1984), 14(3), 227.

4. P. Singh and M. Weinreb, **Tetrahedron**, (1976), 32, 2379.

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