Natural Product Synthesis

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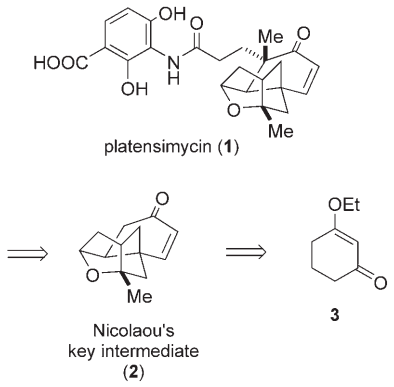
Protecting-Group-Free Formal Synthesis of Platensimycin**

*Konrad Tiefenbacher and Johann Mulzer**

Dedicated to Professor Herbert Mayr on the occasion of his 60th birthday

The ever increasing multiresistance of bacteria is a serious and urgent problem that calls for the introduction of novel antibiotics that do not use established biological targets. In this respect, the discovery of platensimycin (**1**),[1] a metabolite of *Streptomyces platensis*, has been hailed as a true breakthrough in antibiotic research. However, the in vivo efficacy of **1** is low, owing to its limited metabolic stability,[2] so that suitable derivatives of **1** will have to be investigated to find more promising drug candidates. This demand presents a strong motivation for total synthesis.

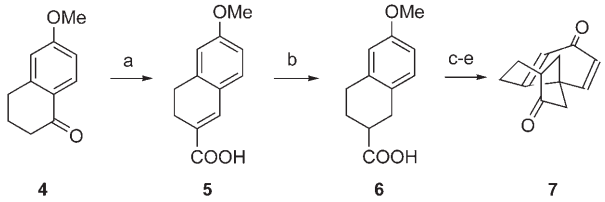
Toward the end of 2006, the Nicolaou group reported the first total synthesis of **1** via compound **2** as a late key intermediate (Scheme 1).[3] Compound **2** was prepared from **3**



Scheme 1. Retrosynthesis of Nicolaou and co-workers.[3,4]

in racemic (10 steps, 11%) and later in optically active form[4] using chiral catalysis (16 steps, 5.6%) or diastereoselective alkylation (11 steps, 8.6%) as key steps. Quite recently, intermediate **2** has also been prepared in racemic form by the Snider group (seven steps + equilibration + one step for conversion of a diastereomer, 32%).[5]

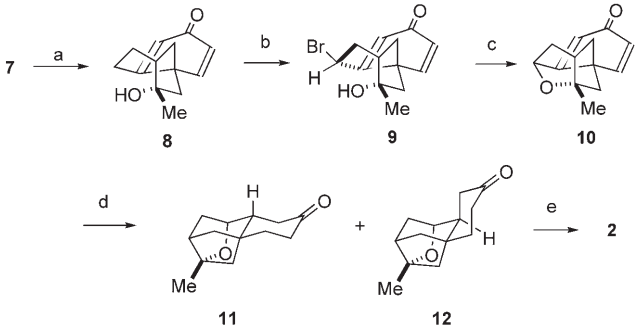
We report a novel route to **2** that starts from known compound **7** (Scheme 2),[6] which is readily available in multigram quantities from inexpensive 6-methoxy-1-tetralone (**4**) in 50% overall yield.[6,7] Intermediates **5**, **6**, and **7** are



Scheme 2. Synthesis of tricycle **7**. Reagents and conditions: a) Three steps (86%; reference [7]: 54%); b) H_2, Pd/C, EtOH (99%; reference [7]: 92%); c) $SOCl_2$, DMF, toluene, RT, 3 h; d) $TMSCHN_2$, THF; hexane/EtOAc (10:1), SiO_2, RT, 12 h; e) TFA, −20°C, 1 h (three steps, 59%). DMF = *N*,*N*-dimethylformamide, TMS = trimethylsilyl, THF = tetrahydrofuran, TFA = trifluoroacetic acid.

crystalline and can be isolated without any chromatography. The catalytic hydrogenation of **5** to **6** might be performed with a chiral catalyst, so that **7** should also be available as either enantiomer. Another option is chiral resolution of carboxylic acid **6**.

Regio- and stereoselective addition of methylmagnesium iodide under carefully controlled conditions converted **7** into alcohol **8** (Scheme 3). Allylic bromination generated bromide **9** stereoselectively, which under basic conditions cyclized to tetrahydrofuran **10**.[8] For the 1,4-reduction of **10** to **12**, Birch conditions, sodium borohydride in methanol, and triethylsilane/trifluoroacetic acid, among other things, were tried without success. Finally, catalytic hydrogenation with Crabtree's catalyst[9] furnished a separable 1.3:1 diastereomeric mixture of **12** and **11**. Selective monooxidation of **12** using an



Scheme 3. Synthesis of Nicolaou's key intermediate (**2**). Reagents and conditions: a) MeMgI, THF, −78°C, 4 h (71% brsm); b) NBS, $(BzO)_2$, CCl_4, reflux, 90 min (75%); c) NaOMe, THF, 0°C, 30 min (80%); d) cat. $[Ir(cod)Py(PCy_3)]PF_6$, H_2 (1 bar), CH_2Cl_2, over night, (78% brsm), **12**/**11** = 1.3:1; alternatively: Pd/C (5%), KOH, EtOH, H_2 (1 bar), 3 h (90%), **12**/**11** = 1:2; e) HIO_3·DMSO, DMSO, cyclohexene, 50°C, 8 h (60%). brsm = based on recovered starting material, NBS = *N*-bromosuccinimide, Bz = benzoyl, cod = cyclooctadiene, Py = pyridine, Cy = cyclohexyl, DMSO = dimethyl sulfoxide.

[*] Dipl.-Ing. K. Tiefenbacher, Prof. Dr. J. Mulzer
Institut für Organische Chemie
Universität Wien
Währinger strasse 38, 1090 Vienna (Austria)
Fax: (+43) 1-4277-52189
E-mail: johann.mulzer@univie.ac.at
Homepage: http://www.univie.ac.at/rg_mulzer/

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iodic acid–dimethyl sulfoxide complex[10] led to **2**, the analytical data of which matched those reported by Nicolaou and co-workers and the Snider group.[3] *Trans*-decalin derivative **11** may be recycled to **10** by more vigorous oxidation using 10 equivalents of HIO_3 at 60 °C overnight.

In conclusion, we have developed a short, simple, and protecting-group-free[11] route to **2** that requires only five steps (overall yield 20%) from easily available intermediate **7**. Work is underway to produce optically pure material and to find novel procedures for converting **2** into platensimycin (**1**) and suitable analogues thereof.

Experimental Section

Physical properties for compounds **10**, **11**, and **2**:

10: $R_f = 0.40$ (silica gel, hexane/EtOAc 1:1); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 6.66$ (d, $J = 10.0$ Hz, 1H), 6.32 (dd, $J = 10.0$, 1.6 Hz, 1H), 6.12 (d, $J = 1.6$ Hz, 1H), 4.71 (d, $J = 4.3$ Hz, 1H), 2.59 (t, $J = 6.2$ Hz, 1H), 2.28–2.14 (m, 2H,), 2.01–1.92 (m, 2H), 1.78 (d, $J = 11.4$ Hz, 1H), 1.56–1.50 (m, 1H), 1.51 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 187.1$, 160.4, 150.9, 130.1, 121.9, 87.1, 80.0, 54.9, 49.9, 48.7, 44.4, 42.6, 22.2 ppm; HRMS (EI) calcd for $C_{13}H_{14}O_2$: 202.0994, found: 202.0990.

11: $R_f = 0.56$ (silica gel, hexane/EtOAc 1:1); ^{1}H NMR (600 MHz, $CDCl_3$): $\delta = 3.97$ (d, $J = 4.5$ Hz, 1H), 2.75 (t, $J = 14.1$ Hz, 1H), 2.34–2.27 (m, 4H), 2.22 (ddd, $J = 14.7$, 4.4, 1.6 Hz, 1H), 2.03–1.99 (m, 1H), 1.83–1.68 (m, 4H), 1.63–1.60 (m, 1H), 1.42 (s, 3H), 1.40 (dd, $J = 11.5$, 3.7 Hz, 1H), 1.23 ppm (d, $J = 11.5$ Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): $\delta = 212.0$, 87.3, 79.8, 47.6, 45.4, 44.9, 44.7, 44.4, 42.7, 41.5, 39.4, 35.0, 23.3 ppm; HRMS (EI) calcd for $C_{13}H_{18}O_2$: 206.1307, found: 206.1304.

2: $R_f = 0.32$ (silica gel, hexane/EtOAc 1:1); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 6.61$ (d, $J = 10.1$ Hz, 1H), 5.94 (d, $J = 10.1$ Hz, 1H), 4.16 (t, $J = 3.5$ Hz, 1H), 2.41–2.28 (m, 4H,), 1.98–1.92 (m, 2H), 1.88 (d, $J = 11.8$ Hz, 1H), 1.79–1.74 (m, 2H), 1.65 (d, $J = 11.3$ Hz, 1H), 1.44 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 199.1$, 155.1, 128.8, 87.1, 78.9, 51.5, 46.1, 44.1, 42.6, 42.2, 37.9, 37.4, 23.1 ppm; HRMS (EI) calcd for $C_{13}H_{16}O_2$: 204.1150, found: 204.1145.

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