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Facile synthesis of caerulomycin E by the formation of 2,2′-bipyridine core via a 2-pyridyl substituted 4*H*-pyran-4-one. Formal synthesis of caerulomycin A

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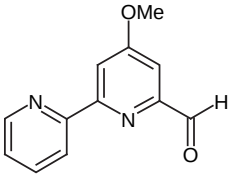
ABSTRACT

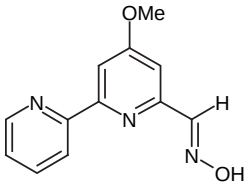
A new approach to caerulomycins A and E via a 6-methyl-2-(2-pyridyl)-4*H*-pyran-4-one is described. The pyranone precursor is prepared by Claisen condensation of acetylacetone enol ether with ethyl picolinate.

1. Introduction

Caerulomycin E (**1**), first isolated and characterized in 1988, is one of the metabolites produced by *Streptomyces caeruleus*.[1] The caerulomycins,[1–3] possessing 2,2′-bipyridinic skeleton, are known to exhibit antiamoebal[4] and antifungal[3] properties. Recently caerulomycin A (**2**), structurally related to compound **1**, has been found to be an effective immunosuppressive agent.[5]



1
Caerulomycin E



2
Caerulomycin A

The considerable biological properties of these natural products together with the constant interest in the development of new synthetic methods for the preparation of functionalized 2,2′-bipyridine derivatives[6] stimulate synthetic studies towards caerulomycins. Several syntheses of caerulomycin E (**1**) have been reported recently, including elaboration of an existing 2,2′-bipyridinic precursor,[7] construction of the caerulomycin skeleton by Pd-mediated cross-coupling reactions[8] or assembling the bipyridinic core from acyclic starting materials.[9]

Previously we have developed an effective synthetic approach to perfluoroalkylated six-membered heterocyclic compounds based on the condensation of ethyl perfluoroalkanoates with 2-acetyloxiranes or enol ethers of β-dicarbonyl compounds leading to corresponding 4*H*-pyran-4-ones.[10] The latter are suitable precursors for a variety of perfluoroalkylated nitrogen-containing heterocycles.[11,12] Our interest in the chemistry of pyranes and pyridines prompted us to apply this methodology for the synthesis of pyridine-containing natural products. We envisaged that synthesis of caerulomycin E molecule starting from appropriate 4*H*-pyran-4-one may be accomplished in a step-economical fashion since this starting material possesses the requisite functionality of the pyridine ring of the target compound **1**. We describe herein concise synthesis of caerulomycin E (**1**) in a four-step sequence starting from easily accessible 4-ethoxy-3-penten-2-one[13,14] (**3**) via 6-methyl-2-(2-pyridyl)-4*H*-pyran-4-one (**5**). The reported synthesis may be regarded as a formal synthesis of caerulomycin A (**2**), the transformation of compound **1** to its congener **2** is well documented in the literature.[7,8]

2. Results and discussion

The key-intermediate in the synthesis of caerulomycin E, 4-methoxypyridine **7**, can be conveniently prepared from the known ethoxypentenone **3** via pyranone **5** following our procedure[10] for 2-perfluoroalkylated congeners. Thus, the reaction of acetylacetone

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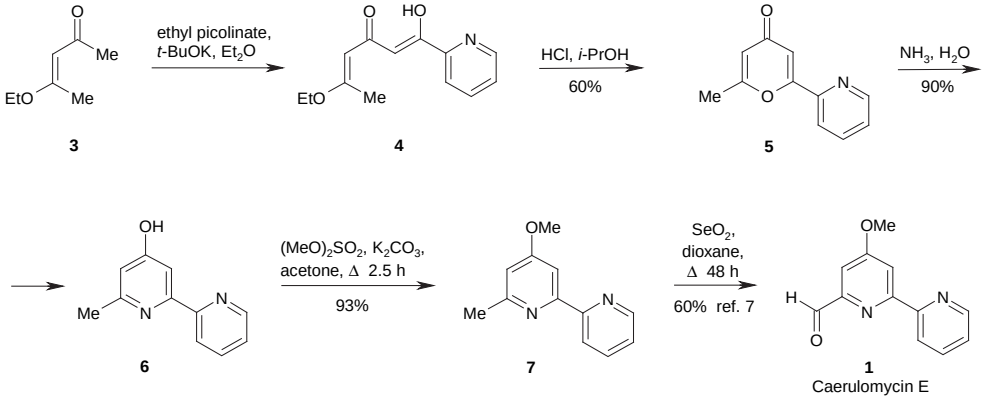
enol ether **3** with ethyl picolinate in the presence of an excess of potassium *tert*-butoxide, followed by acid catalyzed cyclization with hydrochloric acid in boiling *i*-PrOH, afforded 6-pyridyl-substituted pyranone **5** in 60% overall yield. Intermediate diketone **4**, which can be isolated as a bright-yellow crystalline substance, was apparently an unstable compound, gradually transforming on storage into the target pyranone **5** along with other unidentified products.



Treatment of the pyranone **5** with aqueous ammonia at reflux smoothly provided 4-hydroxybipyridine **6** in excellent yield. Subsequent methylation of pyridinol **6** with dimethyl sulfate in acetone produced almost quantitatively the key-intermediate 4-methoxybipyridine **7**. It is noteworthy that formation of possible N-methylation product was not detected under these alkylation conditions. This observation may be attributed to the fact that bipyridine compound **6**, similarly to its 2-perfluoroalkylated analogues, exists predominantly in hydroxy-form rather than the tautomeric 4(1*H*)-pyridinone.[9,11,12,15] Side chain oxidation of 4-methoxybipyridine **7** with SeO_2 in boiling dioxane afforded the target caerulomycin E (**1**).[7]

The present methodology provides a facile, not requiring chromatographic purification, access to the key-intermediate **7** of Quéguiner's synthesis[7,9] in 50% overall yield from the acyclic precursor **3** using inexpensive reagents. Due to its preparative value, this new approach represents a useful complement to the syntheses of caerulomycin E reported recently.[8,9] Moreover, the pyranone intermediate **5** may be transformed into a range of potentially bioactive *N*-substituted bipyridine derivative by reaction with primary amines.[16]

In summary, we have developed an expedient synthesis of caerulomycin E (**1**) in four preparative steps in overall yield 30% starting from easily accessible 4-ethoxy-3-penten-2-one (**3**) via 6-methyl-2-(2-pyridyl)-4*H*-pyran-4-one (**5**).

3. Experimental

3.1. General

IR spectra were measured on a Specord 75 IR spectrophotometer. ^{1}H NMR spectra were recorded on a Bruker Avance 400 (400 MHz) or a Bruker AC-200 (200 MHz) spectrometer. ^{13}C NMR spectra were recorded on a Bruker Avance 400 at 100.6 MHz. Mass spectra were obtained on a Shimadzu QP-5000 GC/MS spectrometer. Melting points were determined in open capillaries and are uncorrected. Preparative column chromatography was carried out on silica gel (Merck; 70–230 mesh). All chemicals were reagent grade; solvents were dried and distilled prior to use.

4-Ethoxy-3-pentene-2-one (**3**) was obtained by a literature method.[14]

3.2. 6-Methyl-2-(2-pyridyl)-4*H*-pyran-4-one (5)

To a vigorously stirred suspension of potassium *tert*-butoxide (3.4 g, 30 mmol) in dry Et_2O (50 mL) was added dropwise the mixture of freshly distilled 4-ethoxy-3-pentene-2-one (**3**) (2.4 g, 19 mmol) and ethyl picolinate (3.4 g, 22 mmol) at −10 °C over 30 min. After the addition was completed, the reaction mixture was stirred for 4 h at 0 °C and for 12 h at 18–20 °C. Then it was quenched by dropwise addition of glacial acetic acid (1.8 mL, 30 mmol) followed by water (15 mL), the aqueous layer was separated and extracted with Et_2O (10 mL×5). The residue after Et_2O evaporation was refluxed for 5 h in isopropyl alcohol (20 mL) in the presence of 36% aqueous HCl (3 mL). After evaporation of *i*-PrOH, the residue was diluted with 10 mL of water, neutralized with solid Na_2CO_3 and extracted with CH_2Cl_2 (10 mL×5). The combined organic phases were washed with brine and dried over Na_2SO_4. After solvent removal the residue was crystallized from toluene–cyclohexane mixture (1:3) to obtain pyranone **5** (2.1 g, 60%) as colourless needles; mp 97–98 °C; IR (CCl_4): 1665, 1635 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.35 (s, 3H, CH_3), 6.15–6.16 (m, 1H, 5-H), 7.22 (d, J=2.3 Hz, 1H, 3-H), 7.35 (ddd, J=1.8, 4.9, 7.2 Hz, 1H, 5′-H), 7.77–7.84 (2H, m, 3′-H+4′-H), 8.64 (1H, d, J=4.9 Hz, 6′-H); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 19.8, 111.9, 115.0, 120.3, 125.2, 136.9, 148.9, 149.9, 161.8, 165.1, 180.1; EIMS (70 eV), *m*/*z* (rel int.): 188 (M^++1, 12), 187 (M^+, 97), 159 (100), 158 (21), 144 (45), 131 (11), 130 (80), 119 (13), 116 (16), 104 (12), 103 (35), 89 (10), 79 (55), 78 (74), 76 (41), 69 (58), 65 (15), 63 (20), 53 (24), 52 (53), 51 (69), 50 (42), 43 (45), 41 (13), 39 (29). Anal. Calcd for $C_{11}H_9NO_2$: C 70.58; H 4.85. Found: C 70.72; H 5.01.

3.3. Isolation of (*E*)-5-ethoxy-1-(2-pyridyl)-4-hexen-1,3-dione (4)

In a similar experiment as described above for preparation of compound **5**, the crude product obtained from 0.5 g (3.9 mmol) of enol ether **3**, without treatment with HCl, was dissolved in hexane–Et_2O mixture (1:1) and passed through a short plug of SiO_2 on a glass filter. The residue after solvent evaporation was crystallized from benzene–hexane mixture (1:10) to afford 0.24 g (26%) of diketone **4** as bright-yellow needles; mp 75–76 °C; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.38 (t, J=7.0 Hz, 3H, CH_3CH_2), 2.41 (s, 3H, CH_3), 3.89 (q, J=7.0 Hz, 2H, CH_3CH_2), 5.37 [s, 1H, *CH*=C(OH)Py], 6.68 [s, 1H, *CH*=C(OEt)CH_3], 7.37 (ddd, J=0.8, 4.6, 7.6 Hz, 1H, 5′-H), 7.82 (td, J=1.6,

7.8 Hz, 1H, 4′-H), 8.05 (d, J=7.8 Hz, 1H, 3′-H), 8.64 (d, J=4.6 Hz, 1H, 6′-H), 16.49 ppm (br s, 1H, OH).

3.4. 4-Hydroxy-6-methyl-2,2′-bipyridine (6)

Mixture of 1.96 g (10 mmol) of pyranone **5** and 5 mL (70 mmol) of 25% aqueous ammonia was heated under reflux for 8 h. After evaporation of the solvent under reduced pressure, the solid residue was recrystallized from dioxane to give 1.75 g (90%) of bipyridine **6** as a white solid; mp 173–174 °C (lit.[17] mp 170–172 °C); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.39 (s, 3H, CH_3), 6.28 (s, 1H, 5-H), 6.95 (s, 1H, 3-H), 7.36 (dd, J=4.8, 8.1 Hz, 1H, 5′-H), 7.80–7.86 (m, 2H, 3′-H+4′-H), 8.61 (d, J=4.6 Hz, 1H, 6′-H), 10.15 (br s, 1H, OH).

3.5. 4-Methoxy-6-methyl-2,2′-bipyridine (7)

A solution of 1.0 g (5.4 mmol) of pyridinol **6** and 0.5 mL (5.4 mmol) of dimethyl sulfate in 20 mL of anhydrous acetone was heated under reflux in the presence of 2.2 g (16.1 mmol) of potassium carbonate for 2 h. After cooling to room temperature the mixture was filtered through a short plug of silica on a glass filter. The residue after solvent removal was crystallized from hexane to provide 1.0 g (93%) of methoxypiridine **7** as white needles; mp 60.5–61.5 °C (lit. mp 57 °C,[7] 53 °C,[9] 59–60 °C[17]); IR (CCl_4): 1600, 1580, 1545 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.52 (s, 3H, CH_3), 3.85 (s, 3H, OCH_3), 6.65 (d, J=2.0 Hz, 1H, 5-H), 7.23 (ddd, J=1.1, 4.6, 7.5 Hz, 1H, 5′-H), 7.71–7.75 (m, 2H, 3-H+4′-H), 8.36 (d, J=8.0 Hz, 1H, 3′-H), 8.61 (d, J=4.6 Hz, 1H, 6′-H); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 24.5, 55.0, 103.4, 109.7, 121.2, 123.5, 136.6, 148.8, 156.1, 157.2, 159.2, 166.8.

3.6. 4-Methoxy-2,2′-bipyridine-6-carbaldehyde (caerulomycin E) (1)

Compound **1** was prepared in 60% yield by oxidation of 4-methoxybipyridine **7** with SeO_2 in boiling dioxane according to the previously reported procedure.[7] Caerulomycin E (**1**), colourless needles (from n-hexane): mp 85–86 °C (lit. mp 80 °C,[7] 83 °C[1]); IR (CCl_4): 1715 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.96 (s, 3H, OCH_3), 7.33 (ddd, J=1.1, 4.8, 7.4 Hz, 1H, 5′-H), 7.45 (d, J=2.3 Hz, 1H, 3-H), 7.83 (td, J=1.5, 7.7 Hz, 1H, 4′-H), 8.14 (d, J=2.6 Hz, 1H, 5-H), 8.50 (d, J=7.9 Hz, 1H, 3′-H), 8.66 (d, J=4.6 Hz, 1H, 6′-H), 10.09 (s, 1H, CHO); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 55.8, 107.6, 110.4, 121.4, 124.3, 137.0, 149.1, 154.0, 154.9, 158.3, 167.5, 193.5; EIMS (70 eV), m/z (rel int.): 215 (M^++1, 14), 214 (M^+, 100), 213 (95), 186 (17), 185 (34), 184 (35), 170 (9), 156 (13), 155 (68), 143 (13), 142 (26), 130 (27), 128 (10), 115 (13), 105 (15), 104 (21), 89 (9), 79 (19), 78 (63), 76 (21), 64 (14), 63 (15), 52 (28), 51 (51), 50 (30), 39 (19).

Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2010.05.030. These data include MOL files and InChiKeys of the most important compounds described in this article.

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