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Eight-Step Synthesis of Routiennocin

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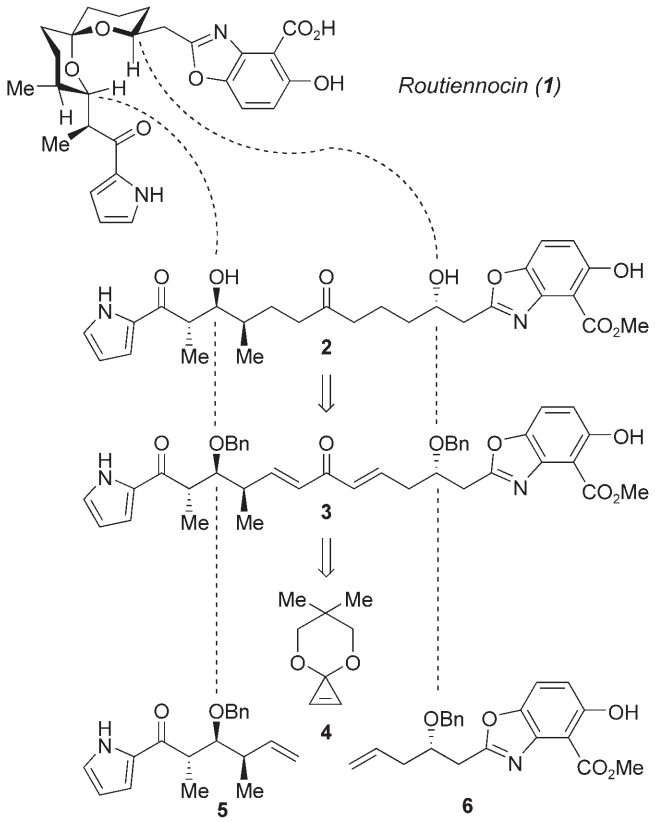
Abstract: Routiennocin is a member of a family of polycyclic pyrrole ether antibiotics that simultaneously uncouple oxidative phosphorylation and inhibit ATPase as a result of selective complexation of divalent metal ions. We describe a concise synthesis of routiennocin with the longest linear sequence of 8 steps. Our synthesis features a unique bi-directional strategy, which entails a sequential ring-opening/cross metathesis of a highly strained cyclopropenone acetal. This approach enables rapid and highly convergent assembly of the fully extended polyketide subunit of this natural product from readily available homoallylic alcohol precursors.

Keywords: antibiotics; asymmetric synthesis; metathesis; natural products; ruthenium; spiro compounds

Polycyclic pyrrole ether antibiotics comprise a family of divalent ionophores produced by different species of *Streptomyces*.[1] Selective complexation of metal ions by this class of natural products has been linked to their ability to simultaneously uncouple oxidative phosphorylation and to inhibit ATPase in rat liver mitochondria.[2] Routiennocin (**1**) is a representative member of this family of antibiotics, which also includes calcimycin (A-23187),[3] cezomycin,[4] X-14885A[5] and AC7230.[6] Routiennocin was originally designated as CP-61,405 and isolated by fermentation of a previously unknown microbial species *Streptomyces routienii* Huang sp. nov. (ATCC 39446).[7] The natural product was found to display potent activity against a wide spectrum of Gram-positive and anaerobic bacteria.[7] Structural analysis of routiennocin revealed the presence of carboxylic acid, benzoxazole and ketopyrrole groups. The three functional groups comprise the ionophore subunit, that enables tridentate coordination of divalent cations, such as Mn^{2+}, Ca^{2+}, Mg^{2+}, Fe^{2+}, resulting in the formation of octahedral 2:1 complexes.[8–13] Such effective scavenging of metal ions perturbs normal mitochondrial function by altering the endogenous levels of calcium and magnesium.[2] The unique biochemistry of pyrrole ether antibiotics stimulated considerable interest in the assembly of this class of natural products, which enabled one to test the power of synthetic methods for the construction of polyketide-derived spiroketals.[14] Several syntheses of calcimycin have been reported by Evans,[15] Grieco,[16] Ogawa,[17] Kishi,[18] Boeckman[19] and Ziegler.[20] In contrast to calcimycin, the only synthesis of routiennocin was described by Ley and coworkers in 1992.[21] The assembly of the spiroketal was based on the sulfone alkylation tactic and delivered the final target with the longest linear sequence of 16 steps.

We have recently devised a highly convergent strategy for polyketide assembly, which exploits the unique reactivity of cyclopropenone acetals in providing rapid synthetic access to spiroketal-containing natural products, such as bistramide A[22] and spirofungin A.[23] Herein, we provide another important demonstration of the generality and the convergency of our metathesis-based strategy by describing the development of a concise synthesis of routiennocin. The assembly process takes a full advantage of the exceptional functional group compatibility of Ru-based olefin metathesis[24] in enabling coupling of complex synthetic fragments *en route* to the final target, which is assembled with the longest linear sequence of only 8 steps.

Our strategy for the rapid assembly of routiennocin (**1**) is outlined in Scheme 1. The unique feature of our approach is the assembly of a fully elaborated spiroketalization precursor **2** containing both heterocyclic subunits prior to the spiroketalization event. This strategy was expected to significantly facilitate the end game of the synthesis, providing a fully convergent entry to the final target **1**. Ketone **2** would derive from dienone **3** by hydrogenation and concomitant hydrogenolysis of two benzyl ethers. The assembly of dienone **3** would entail a sequential ring-opening/cross metathesis of highly strained cyclopropenone acetal **4** with terminal alkenes **5** and **6**. The most

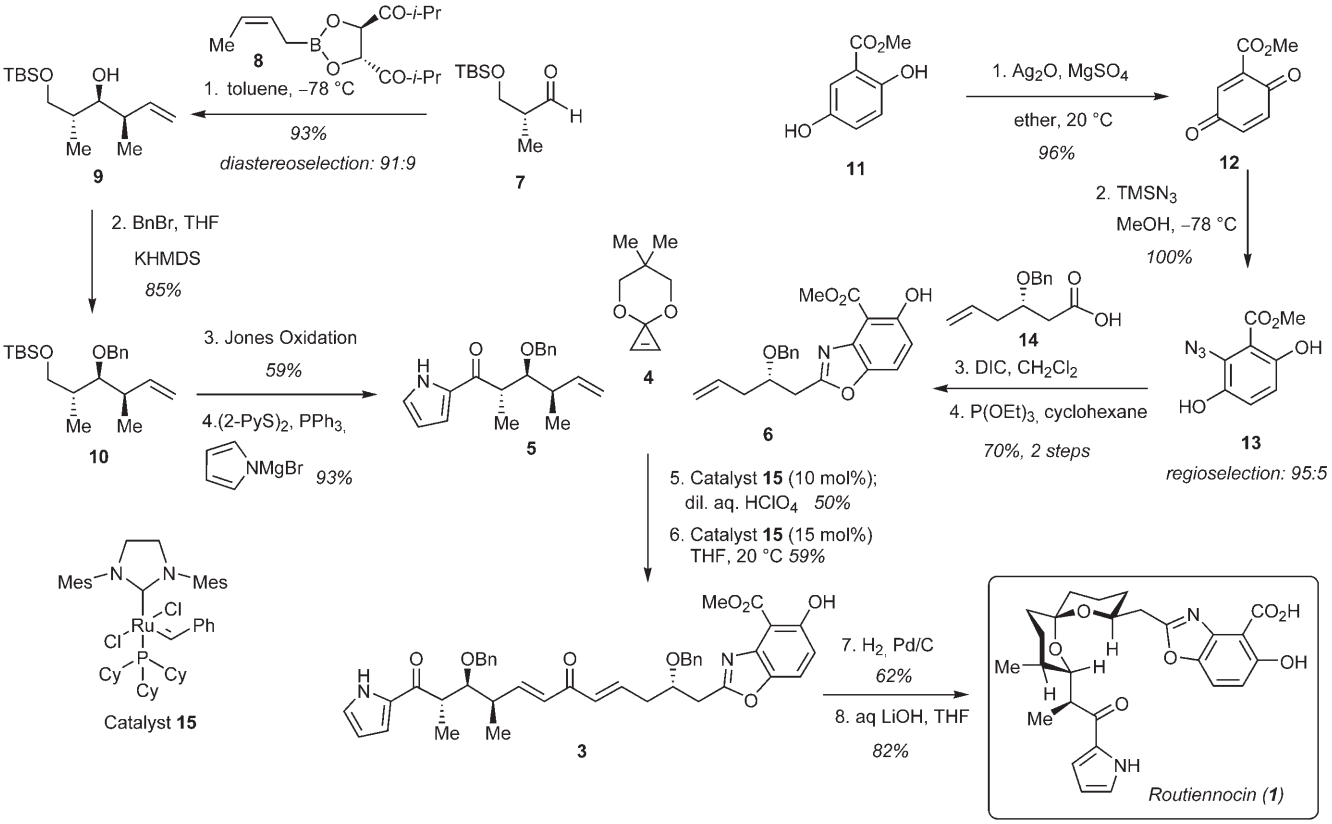


Scheme 1. Retrosynthetic analysis of routiennocin (**1**).

challenging aspect of the synthesis entailed developing an efficient set of conditions that would enable the coupling of **5** and **6** in the presence of fully elaborated heterocyclic moieties.

The synthesis began with Roush crotylboration[25] of a well-known aldehyde **7**[26] to give alcohol **9** in 93% yield and a diastereoselection of 91:9 (Scheme 2). Treatment of alcohol **9** with KHMDS and BnBr furnished the requisite benzyl ether **10**. Jones oxidation of the primary TBS ether, followed by conversion of the resulting carboxylic acid to the corresponding thiopyridyl ester and *in situ* addition of the pyrrolemagnesium bromide delivered the first requisite alkene **5** (4 steps, 46% overall yield).[27]

Assembly of the second metathesis partner **6** commenced with oxidation of hydroquinone **11** to quinone **12** with silver oxide (96% yield). Regioselective installation of the azide moiety was realized by treating quinone **12** with $TMSN_3$ in MeOH at −78 °C. Diol **13** was next coupled with carboxylic acid **14**, which was prepared in 3 steps by Keck allylation[28] of 3-(*tert*-butyldimethylsiloxy)propanal, followed by benzylation of the homoallylic alcohol and Jones oxidation of primary silyl ether. Subsequent treatment of the resulting ester with $P(OEt)_3$ in THF triggered the intramolecular Staudinger reaction to give benzoxazole **6** (70% yield, 2 steps).[29]



Scheme 2. Eight-step synthesis of routiennocin (**1**).

The final metathesis sequence began with the ring-opening of cyclopropenone acetal **4**[30] with alkene **5** in the presence of Grubbs' catalyst **15**.[31] Following the *in situ* removal of the acetal under acidic conditions, which is required to enable the second productive metathesis step, the resulting enone was treated with the benzoxazole-contaning alkene **6**, again in the presence of catalyst **15**, to deliver the fully extended enone **3**. Subjection of dienone **3** to heterogeneous hydrogenation with concomitant hydrogenolysis of benzyl ethers, followed by saponification of the methyl ester according to the Ley's protocol[21] delivered the final target (**1**). The 500 MHz ^{1}H NMR and 125 MHz ^{13}C NMR spectra of synthetic routiennocin (**1**), as well as the optical rotation were in excellent agreement with those reported previously.[7,21]

In closing, we have developed a concise synthetic access to routiennocin (**1**) with a longest linear sequence of 8 steps, which significantly exceeds the efficiency of any of the existing synthetic approaches to naturally occurring polycyclic pyrrole ether antibiotics. Such rapid assembly of routiennocin provides another demonstration of the power of the cyclopropenone acetal metathesis-based strategy for rapid assembly of complex spiroketal-containing natural products.

Experimental Section

Ring-Opening/Cross Metathesis Sequence

Grubbs' catalyst **15** (25 mg, 0.030 mmol) was dissolved in anhydrous THF (2 mL) and treated dropwise with solution of alkene **5** (90 mg, 0.30 mmol) and cyclopropenone acetal **4** (84 mg, 0.60 mmol) in THF (3 mL) at room temperature. After 1.5 h, the reaction mixture was cooled to 0 °C, treated with $HClO_4$ (0.050 mL, 30% solution in water) and stirred for 10 min at 0 °C until TLC indicated complete consumption of the starting material. The reaction mixture was quenched with saturated $NaHCO_3$ solution and diluted with ethyl acetate-hexane. The resulting mixture was washed with brine and dried over $MgSO_4$. The solvent was evaporated and the residue was purified by flash chromatography on silica gel (ethyl acetate: hexane = 1:5 to 1:3) to give the corresponding dienone as a pale brown oil; yield: 53 mg (50%). For complete analytical characterization, see Supporting Information.

Next, Grubbs' catalyst **15** (13 mg, 0.015 mmol) and the above dienone (64 mg, 0.18 mmol) were dissolved in THF (2 mL) and treated dropwise (30 min) with a solution of alkene **6** (38 mg, 0.10 mmol) in THF (3 mL) at room temperature. After 6 h, the solvent was removed under vacuum and the residue was purified by flash chromatography on silica gel (ethyl acetate: hexane = 1:1) to yield dienone **3** as a brown oil; yield: 42 mg (59%). For complete analytical characterization, see Supporting Information.

Routiennocin Methyl Ester (23)

A solution of dienone **3** (80 mg, 0.12 mmol) in methanol (2 mL) was treated with Pd-C (25 mg, 10 wt%) and stirred at room temperature for 7 h under an atmosphere of H_2 (1 atm). The resulting mixture was filtered and the filtrate was concentrated under vacuum and the residue was purified by preparative TLC (ethyl acetate:hexane = 1:1) to afford routiennocin methyl ester **23** as a pale brown foam; yield: 36 mg (62%). For complete analytical characterization, see Supporting Information.

Routiennocin (1)

A solution of routiennocin methyl ester **23** (10 mg, 0.020 mmol) in THF-H_2O (10:1, 1 mL) was treated with lithium hydroxide monohydrate (14 mg, 0.33 mmol) and stirred at room temperature for 48 h. The reaction mixture was acidified by careful addition of 2 N HCl and then diluted with chloroform. The resulting mixture was washed with H_2O and brine, dried over Na_2SO_4. The solvent was evaporated and the residue was chromatographed over silica gel (ethyl acetate: Et_2O = 1:5) to afford carboxylic acid **1** as a colorless form; yield: 8.0 mg (82%). For complete analytical characterization, see Supporting Information.

Supporting Information

Full characterization of all new compounds and experimental procedures are given in the Supporting Information.

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References

[1] a) J. W. Westley, *Polyether Antibiotics*, Vols. 1 and 2, Marcel Dekker, New York, **1982**; b) J. W. Westley, *J. Nat. Prod.* **1986**, *49*, 35–47; c) C. J. Dutton, B. J. Banks, C. B. Cooper, *Nat. Prod. Rep.* **1994**, *12*, 165–181.
[2] P. W. Reed, H. A. Lardy, *J. Biol. Chem.* **1972**, *247*, 6970–6977.
[3] M. O. Chaney, P. V. Demarco, N. D. Jones, J. L. Ocvolowitz, *J. Am. Chem. Soc.* **1974**, *96*, 1932–1933.
[4] L. David, A. Kergomard, *J. Antibiot.* **1982**, *35*, 1409–1411.
[5] J. W. Westly, C. M. Liu, J. F. Blount, L. H. Shello, N. Troupe, P. A. Miller, *J. Antibiot.* **1983**, *36*, 1275–1278.
[6] S. Yaginuma, M. Awata, N. Muto, K. Kinoshita, *J. Antibiot.* **1987**, *40*, 239–241.
[7] W. D. Cullen, W. D. Celmer, L. R. Chappel, L. H. Huang, M. T. Jefferson, M. Ishiguro, H. Maeda, S. Nishiyama, J. R. Oscarson, R. Shibakawa, J. Tone, *J. Ind. Microbiol.* **1988**, *2*, 349–357.
[8] a) G. D. Smith, W. L. Duax, *J. Am. Chem. Soc.* **1976**, *98*, 1578–1580; b) M. O. Chaney, N. D. Jones, M. Debono, *J. Antibiot.* **1976**, *29*, 424–427.

[9] E. Baker, E. N. Maslen, K. J. Watson, A. H. White, *J. Am. Chem. Soc.* **1984**, *106*, 2860–2864.
[10] M. Alleaume, Y. Barrans, *Can. J. Chem.* **1985**, *63*, 3482–3491.
[11] A. M. Albrecht-Gary, S. Blanc-Parasote, D. W. Boyd, G. Dauphin, G. Jeminet, J. Julliard, C. Tissier, *J. Am. Chem. Soc.* **1989**, *111*, 8598–8609.
[12] W. L. Erdahl, C. J. Chapman, R. W. Taylor, D. R. Pfeiffer, *Biophy. J.* **1994**, *66*, 1678–1693.
[13] a) S. Vila, I. Canet, J. Guyot, G. Jeminet, L. Toupet, *Chem. Commun.* **2003**, 516–517; b) W. L. Erdahl, C. J. Chapman, E. Wang, R. W. Taylor, D. R. Pfeiffer, *Biochemistry* **1996**, *35*, 13817–13825; c) M. Debono, R. M. Molloy, D. E. Dorman, J. W. Paschal, D. F. Babcock, C. M. Deber, D. R. Pfeiffer, *Biochemistry* **1981**, *20*, 6865–6872.
[14] M. M. Faul, B. E. Huff, *Chem. Rev.* **2000**, *100*, 2407–2473.
[15] D. A. Evans, C. E. Sacks, W. A. Kleschick, T. R. Taber, *J Am. Chem. Soc.* **1979**, *101*, 6789–6791.
[16] a) P. A. Greico, E. Williams, H. Tanaka, S. Gilman, *J. Org. Chem.* **1980**, *45*, 3537–3539; b) G. R. Martinez, P. A. Grieco, E. Williams, K. Kanai, C. V. Srinivasan, *J. Am. Chem. Soc.* **1982**, *104*, 1436–1438.
[17] a) Y. Nakahara, K. Beppu, T. Ogawa, *Tetrahedron Lett.* **1981**, *22*, 3197–3200; b) Y. Nakahara, A. Fujita, K. Beppu, T. Ogawa, *Tetrahedron* **1986**, *42*, 6465–6476; c) Y. Nakahara, A. Fujita, T. Ogawa, *J. Carbohydr. Chem.* **1984**, *3*, 487–492.
[18] D. P. Negri, Y. Kishi, *Tetrahedron Lett.* **1987**, *28*, 1063–1066.
[19] a) R. K. Boeckman, Jr., A. B. Charette, T. Asberom, B. H. Johnston, *J. Am. Chem. Soc.* **1987**, *109*, 7553–7555; b) R. K. Boeckman, Jr., A. B. Charette, T. Asberom, B. H. Johnston, *J. Am. Chem. Soc.* **1991**, *113*, 5337–5353.
[20] F. E. Ziegler, W. T. Cain, *J. Org. Chem.* **1989**, *54*, 3347–3353.
[21] a) N. R. Kotecha, S. V. Ley, S. Mantegami, *Synlett* **1992**, 395–399; b) D. Diez-Martin, N. R. Koetcha, S. V. Ley, J. C. Menendez, *Synlett* **1992**, 399–401; c) D. Diez-Martin, N. R. Koetcha, S. V. Ley, S. Mantegami, J. C. Menendez, H. M. Organ, A. D. White, *Tetrahedron* **1992**, *48*, 7899–7938.
[22] A. V. Statsuk, D. Liu, S. A. Kozmin, *J. Am. Chem. Soc.* **2004**, *126*, 9546–9547.
[23] J. Marjanovic, S. A. Kozmin, *Angew. Chem. Int. Ed.* **2007**, *46*, 9010–9013.
[24] T. M. Trnka, R. H. Grubbs, *Acc. Chem. Res.* **2001**, *34*,18–29.
[25] a) W. R. Roush, K. Ando, D. B. Powers, A. D. Palkowitz, R. L. Halterman, *J. Am. Chem. Soc.* **1990**, *112*, 6339–6348; b) W. R. Roush, A. D. Palkowitz, K. Ando, *J. Am. Chem. Soc.* **1990**, *112*, 6348–6359.
[26] J. Cossy, D. Bauer, V. Bellosta, *Tetrahedron* **2002**, *58*, 5909–5922.
[27] K. C. Nicolaou, D. A. Calaremon, D. P. Papahatjis, *Tetrahedron Lett.* **22**, *1981*, 4647–4650.
[28] a) G. E. Keck, K. H. Tarbet, L. S. Geraci, *J. Am. Chem. Soc.* **1993**, *115*, 8467–8468; b) M. Kurosu, M. Lorca, *Synlett* **2005**, 1109–1112.
[29] H. Takeuchi, S. Yanagida, T. Ozaki, S. Hagiwara, S. Eguchi, *J. Org. Chem.* **1989**, *54*, 431–434.
[30] M. Nakamura, X. Q. Wang, M. Isaka, S. Yamago, E. Nakamura, *Org. Syn.* **2003**, *80*, 144–151.
[31] M. Scholl, S. Ding, C. W. Lee, R. H. Grubbs, *Org. Lett.* **1999**, *1*, 953–956.

