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# A Concise Total Synthesis of (±)- and (−)-Okilactomycin D

**Dawen Niu and Thomas R. Hoye***

*Department of Chemistry, University of Minnesota, Minneapolis, Minnesota 55455, United States*

*hoye@umn.edu*

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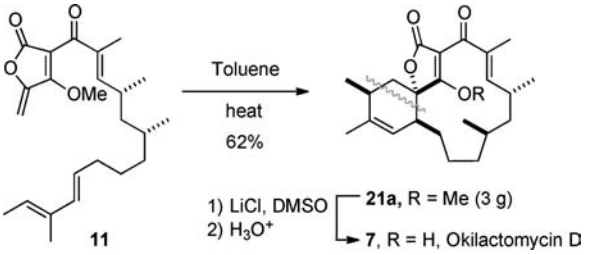
## ABSTRACT




**The spirotetronate okilactomycin D (7) has been efficiently synthesized by a route featuring a substrate-controlled, diastereoselective (8:1) intramolecular Diels–Alder (IMDA) reaction of 11. The assigned absolute configuration of (−)-7 was confirmed.**

The spirotetronate polyketides (e.g., chlorothricolides, kijanimicin, and abyssomicins) comprise a class of natural product compounds that are characterized by the presence of a five-membered tetronic acid moiety spiro-linked to a cyclohexene ring (cf. **1**, Figure 1). Their biological activities (which include antitumor,[1] antimicrobial,[2] and cholesterol biosynthesis inhibition[3]) coupled with unusual architectures render them interesting targets for synthesis.

The okilactomycins (**2** and **4**–**7**), a subclass of spirotetronates, contain either a tri- or tetracyclic skeleton. In 1987 Imai and co-workers reported the isolation and structural elucidation of okilactomycin (**2**) from *Streptomyces griseoflavus*.[4] In 2001 Yamashita and co-workers described the isolation of the structurally related chrolactomycin (**3**) from *Streptomyces* sp. 569N-3.[5] In 2009 Singh et al. reported the isolation of four new members of this class, namely, okilactomycins A, B, C, and D (**4**–**7**) [along with okilactomycin (**2**)] from the bacterium *Streptomyces scabrisporus*.[6] Whereas congeners **6** and **7** contain an intact acyltetronic acid structural subunit,[7] compounds **2**–**5** have a modified tetronate moiety. The structure of each of the new compounds **4**–**7** was assigned based upon spectroscopic analysis. The absolute configurations were assumed

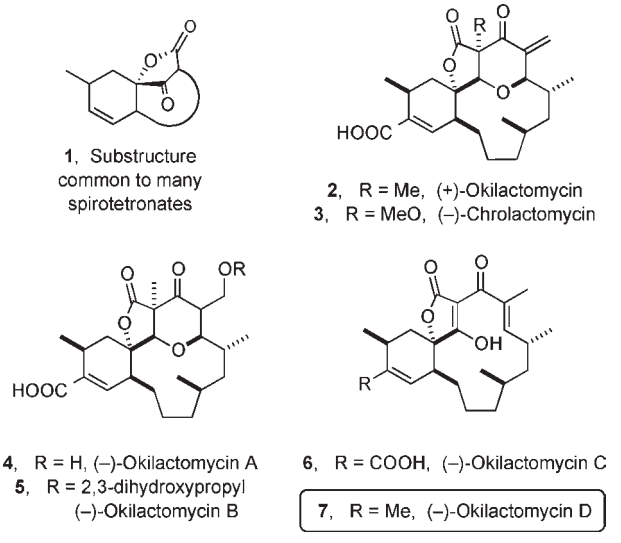



**Figure 1.** Structures of okilactomycins and chrolactomycin.

(1) Kang, M.; Jones, B. D.; Mandel, A. L.; Hammons, J. C.; DiPasquale, A. G.; Rheingold, A. L.; La Clair, J. J.; Burkart, M. D. *J. Org. Chem.* **2009**, *74*, 9054–9061.

(2) Igarashi, Y.; Ogura, H.; Furihata, K.; Oku, N.; Indananda, C.; Thanmchaipenet, A. *J. Nat. Prod.* **2011**, *74*, 670–674.

(3) Kawashima, A.; Nakamura, Y.; Ohta, Y.; Akama, T.; Yamagishi, M.; Hanada, K. *J. Antibiot.* **1992**, *45*, 207–212.

(4) Imai, H. S.; Suzuki, K. I.; Morioka, M.; Numasaki, Y.; Kadota, S.; Nagai, K.; Sato, T.; Iwanami, M.; Saito, T. *J. Antibiot.* **1987**, *40*, 1475–1482.

(5) Nakai, R.; Kakita, S.; Asai, A.; Chiba, S.; Akinaga, S.; Mizukami, T.; Yamashita, Y. *J. Antibiot.* **2001**, *54*, 836–838.

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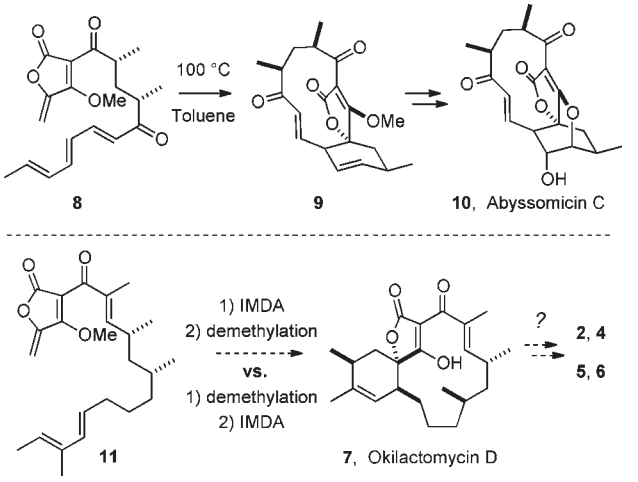
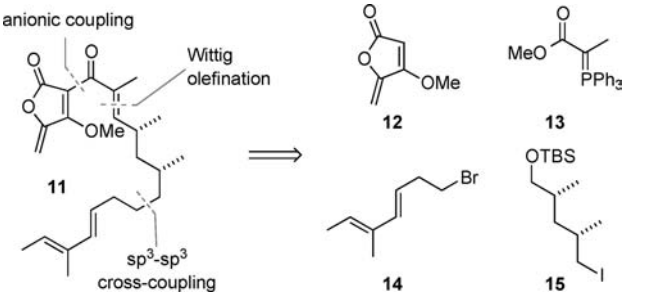
to be the same as that of okilactomycin (**2**), which had been established by the total syntheses achieved in the Smith and Scheidt laboratories.[8] Notably, the sign of the specific rotation of each of **4**–**7** is negative, while that of okilactomycin itself (**2**) is positive, regardless of its producing organism (*Streptomyces griseoflavus*[4] or *Streptomyces scabrisporus*[6]). Whether or not all members of the okilactomycin family are of the same antipodal series has interesting biosynthetic connotations.

**Scheme 1.** IMDAs in Reported Total Syntheses of Abyssomicin C (**10**)[11] *vs* Our Planned Okilactomycin D (**7**) Synthesis




With respect to biosynthesis, it has been proposed that some of the spirotetronate natural products derive from an intramolecular Diels–Alder like (IMDA) macrocyclization.[9,10] This IMDA strategy enabled several remarkably efficient total syntheses of abyssomicin C (**10**).[11] Cyclization of trienone **8** proceeded with high yield and diastereoselectivity, resulting in the construction of the macrocyclic spirotetronate **9** (Scheme 1).[12] Conceivably, the macrocycle in okilactomycin D (**7**) may be generated by a similar IMDA reaction from **11**. However, substrates **11** and **8** differ in both chain length (13- vs 11-membered macrocycle) and electronic character of their diene/dienophile partners. We were interested in how such differences would influence both the rate and diastereoselectivity of this IMDA reaction and, hence, pursued the studies described here. We also note the possibility that **7** could serve as the biogenetic precursor to each of the other okilactomycins (**2** and **4**–**6**) by undergoing post-IMDA modifications. This thinking is consistent with the co-occurrence of **7** with these more highly oxidized okilactomycin members in *Streptomyces scabrisporus*.[6]

**Scheme 2.** Retrosynthetic Plan for Accessing **11**




We planned to assemble **11** from the four building blocks **12**–**15** shown in Scheme 2. Thus, we undertook coupling of the Grignard reagent derived from **14** with iodide **15**, Wittig olefination of an elaborated aldehyde with ylide **13**, and electrophilic net acylation of the lithium anion of methyl tetronate **12**.

The efficient construction of key intermediate **11** is summarized in Scheme 3. Cyclopropyl magnesium bromide (prepared from **16**) was added to tiglic aldehyde, to give cyclopropyl alcohol **17**, which, without purification, was treated with concentrated hydrobromic acid to provide the dienyl bromide **14** (ca. 16:1 ratio of 2*E*,4*E*- and 2*Z*,4*E*-isomers).[13] The Grignard reagent derived from **14** was cross-coupled, under the action of $Li_2CuCl_4$, with known iodide (±)-**15**[14] to give, following TBS ether cleavage, diene **18** (92% yield from **15**) with a ca. 13:1 *E*/*Z* ratio at the terminal double bond.[15] Swern oxidation gave aldehyde **19** in 85% yield. Wittig olefination by the stabilized ylide **13**[16] and standard processing of the resulting enoate (DIBAL-H reduction and $MnO_2$ oxidation)

(6) Zhang, C.; Ondeyka, J.; Zink, D.; Basilio, A.; Vicente, F.; Salazar, O.; Genilloud, O.; Dorso, K.; Motyl, M.; Byrne, K.; Singh, S. *J. Antibiot.* **2009**, *62*, 55–61.

(7) The structure for **7** is arbitrarily (and for convenience) portrayed as an endocyclic enol; an internally hydrogen-bonded variant of that endocyclic enol (a rotamer about the C10–C11 bond) or *E*- or *Z*-exocyclic enols are also possible.

(8) (a) Smith, A. B.; Basu, K.; Bosanac, T. *J. Am. Chem. Soc.* **2007**, *129*, 14872–14874. (b) Smith, A. B.; Bosanac, T.; Basu, K. *J. Am. Chem. Soc.* **2009**, *131*, 2348–2358. (c) Tenenbaum, J. M.; Morris, W. J.; Custar, D. W.; Scheidt, K. A. *Angew. Chem., Int. Ed.* **2011**, *50*, 1–5.

(9) Zhang, H.; White-Phillip, J.; Melançon, C.; Kwon, H.; Yu, W.; Liu, H. *J. Am. Chem. Soc.* **2007**, *129*, 14670–14683.

(10) Jia, X.; Tian, Z.; Shao, L.; Qu, X.; Zhao, Q.; Tang, J.; Tang, G.; Liu, W. *Chem. Biol.* **2006**, *13*, 575–585.

(11) (a) Zapf, C. W.; Harrison, B. A.; Drahl, C.; Sorensen, E. J. *Angew. Chem., Int. Ed.* **2005**, *44*, 6533–6537. (b) Snider, B. B.; Zou, Y. *Org. Lett.* **2005**, *7*, 4939–4941. (c) Couladouros, E. A.; Bouzas, E. A.; Magos, A. D. *Tetrahedron* **2006**, *62*, 5272–5279.

(12) Other IMDA attempts have been reported too. For example: (a) Takeda, K.; Shimotani, A.; Yoshii, E *Heterocycles* **1992**, *34*, 2259–2261. (b) Takeda, K.; Igarashi, Y.; Okazaki, K.; Yoshii, E.; Yamaguchi, K. *J. Org. Chem.* **1990**, *55*, 3431–3434.

(13) Jung, M. E.; Miller, S. J. *Heterocycles* **1990**, *30*, 839–853.

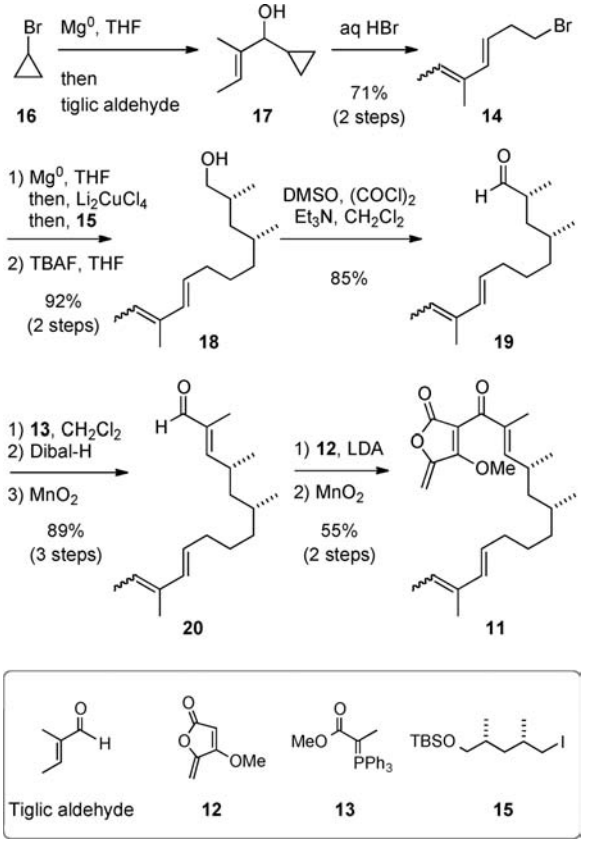
(14) Racemic **15** was synthesized in three steps (see Supporting Information) from the easily accessible[14a,b] (or commercially available) *cis*-3,5-dimethyl glutaric anhydride. Enantiomerically pure **15** was prepared in five steps[14c] from this same anhydride. Racemic **15** was used to pioneer the initial route because of its easier availablity. (a) Paquette, L. A.; Boulet, S. L. *Synthesis* **2002**, 888–894. (b) Prusov, E.; Rohm, H.; Maier, M. E. *Org. Lett.* **2006**, *8*, 1025–1028. (c) Takagi, R.; Tsuyumine, S.; Nishitani, H.; Miyanaga, W.; Ohkata, K. *Aust. J. Chem.* **2004**, *57*, 439–447.

(15) Isomerization of the terminal double bond may derive from a cyclopropane ring-forming, bond rotation, ring-opening sequence. For example, see: Tan, Z.; Negishi, E. *Org. Lett.* **2006**, *8*, 2783–2785.

(16) Smonou, I.; Khan, S.; Foote, C. S.; Elemes, Y.; Mavridis, I. M.; Pantidou, A.; Orfanopoulos, M. *J. Am. Chem. Soc.* **1995**, *117*, 7081–7087.

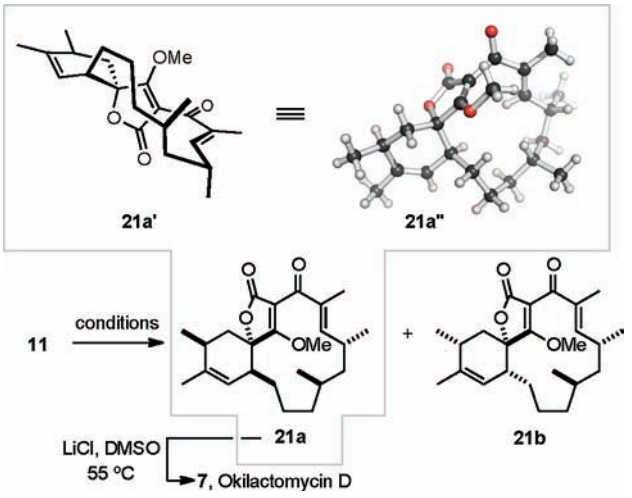
provided enal **20** in 89% yield over three steps. The protocol of Pattenden[17] (as successfully implemented in the abyssomicin C studies[11]) was used to effect anionic addition of lithiated methyl tetronate **12**[18] to **20**. $MnO_2$ oxidation yielded acyltetronate **11** in 55% yield over two steps (60% brsm). All the above reactions were performed at decagram scales.

**Scheme 3.** Synthesis of Acyltetronate **11**




We were pleased to observe that a sample of **11** stored as a solution in $CH_2Cl_2$ at room temperature for several weeks had spontaneously undergone ca. 10% conversion to **21a** (Table 1, entry 1). The relative configuration of this product was identical to that in okilactomycin D (**7**), as shown by subsequent single crystal X-ray crystallographic analysis (cf. Table 1 graphic, **21a**′ and **21a**″). The IMDA reaction of **11** was driven to completion by heating in toluene at 110 °C for 4 days.[19] Careful chromatographic analysis and purification (MPLC on silica gel) provided pure *O*-methyl okilactomycin D (**21a**) as the dominant diastereomer in 62% yield, along with a mixture of three additional, coeluting, minor isomers.[20] Vapor diffusion crystallization (ethyl acetate vs cyclohexane, Supporting Information) enabled isolation of the second most dominant component, **21b**, from this mixture, and its relative configuration was also determined through X-ray crystallographic analysis. The major and minor isomers from these reactions—**21a** and **21b**, respectively, arise from endo vs exo (with respect to the endocyclic furanone alkene) addition of the diene to the dienophilic exomethylene group.

**Table 1.** IMDA Reaction of **11**: Conditions and Outcomes




| entry | conditions[a] | time | **21a:21b**[b] | yield [%] (of **21a**) |
|---|---|---|---|---|
| 1 | $CH_2Cl_2$, rt | 30 d | n.o.[c] | 10[d] |
| **2** | **Toluene, 110 °C** | **96 h** | **8:1** | **62** |
| 3 | $CH_3OH/H_2O$, 90 °C | 6 h | 8:1 | 30–55 |

[a] Reactions were carried out at 0.01 M concentration. [b] Product ratios are determined by $^1$H NMR analysis. [c] Not observed. [d] Ca. 10% conversion based on $^1$H NMR analysis.

It is noteworthy that use of a protic solvent (2:1 MeOH/$H_2O$) accelerated the rate of the IMDA reaction[21] of **11**. In situ $^1$H NMR monitoring indicated that the reaction in a 2:1 $d_4$-methanol/$D_2O$ solution at 90 °C was ca. 30 times faster than that in $d_8$-toluene at 110 °C. The reaction in this protic medium proceeded with a similar level of diastereoselectivity as in toluene, but with a lower yield of isolable material (Table 1, cf. entry 2 vs 3).

(17) Clemo, N. G.; Pattenden, G. *Tetrahedron Lett*. **1982**, *23*, 585–588.

(18) Montgomery, L. J.; Challis, G. L. *Synlett* **2008**, 2164–2168.

(19) Compound **11** has been demethylated under standard conditions (LiCl, DMSO, 50 °C, 4 h). The resulting tetronate anion was found to be inert, even at elevated temperatures (sealed vial: $d_6$-DMSO or $CDCl_3$ at 100 °C, $d_8$-PhMe at 150 °C, and $CD_3OD$ or $D_2O$ at 175 °C). On the other hand, the neutral tetronic acid decomposed (as evidenced by broadening over time of resonances throughout the $^1$H NMR spectrum) before giving any evidence of cyclization to a discrete compound.

(20) It is relevant that the minor 2*Z*,4*E*-diene isomer (**28-*Z***) was typically observed in the crude IMDA reaction product mixture, and it was isolated and characterized from a thermal reaction in toluene (Supporting Information). Thus, the *E*-isomer **28-*E*** reacts faster than **28-*Z***, which is consistent with the expectation/assumption that this IMDA is a concerted process.

(21) Blokzijl, W.; Blandamer, M. J.; Engberts, J. B. F. N. *J. Am. Chem. Soc*. **1991**, *113*, 4241–4246.

To complete the total synthesis of okilactomycin D (**7**), the methyl ether **21a** (200 mg) was dissolved in DMSO (15 mL) and LiCl (15 equiv) was added (Table 1 graphic). Once the mixture became homogeneous, the solution was warmed to 55 °C for 48 h. Partitioning between water and ethyl acetate and washing the organic phase with brine resulted in isolation of the conjugate base of okilactomycin D (**7**), presumably as its sodium salt (see **S-5** in Supporting Information). Alternatively, partitioning of the initial reaction mixture between 10% HCl (aq) and ethyl acetate cleanly gave okilactomycin D (**7**) directly as the neutral acyltetronic acid.

We then synthesized enantiomerically enriched **7**, starting from the nonracemic 5-iodopentane derivative (+)-(2*R*,4*S*)-**15**.[14c] The resulting synthetic sample of okilactomycin D gave essentially identical $^{1}H$ and $^{13}C$ NMR spectral data and had the same sign of optical rotation as that of the natural sample[22] {$[\alpha]_{D\text{synthetic}} = -32$ ($c$ = 0.3, MeOH); lit.[6] $[\alpha]_{D\text{natural}} = -50$ ($c$ = ca. 0.1, MeOH)}, supporting the assigned absolute configuration of (−)-**7** (cf. Figure 1).

In summary, we have demonstrated that the IMDA reaction of **11** is well-suited for construction of the macrocyclic ring in okilactomycins. This has enabled a scalable and efficient synthesis (ca. 17% overall yield) of (±)-okilactomycin D (**7**) comprising 17 steps (13 in its longest linear sequence) from commercially available starting materials. Synthesis of nonracemic (−)-**7** corroborated the assigned absolute configuration of the natural material, thereby establishing that, indeed, okilactomycin [(+)-**2**] and okilactomycin D [(−)-**7**] share the same absolute configuration but differ in the sign of their optical rotation. Given the ready availability of ample quantities of late stage intermediates, we are studying other transforming reactions with an eye toward accessing additional members of the okilactomycin family.

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**Supporting Information Available.** Experimental procedures and spectral data for all new compounds are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

(22) The sample of natural okilactomycin D was isolated after a final purification by HPLC using an eluent doped with trifluoroacetic acid. Thus, its structure is best formulated as **7**, having the neutral acyltetronic acid. We observed that the $^{1}H$ NMR spectrum of the sodium salt **S-5** in $CD_3OD$ (or of the analogous cesium salt in $CDCl_3$) contained a resonance for the enone $\beta$-proton (H6) that was ca. 0.6 (or 0.2) ppm upfield of that for the sample of neutral **7** (see Supporting Information).