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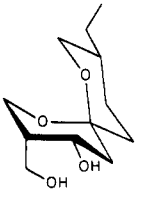
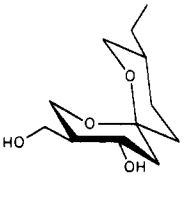
An Enantioselective Total Synthesis of (–)-Talaromycins A and B

Summary: The first enantioselective total synthesis of (–)-talaromycin A and B from a common advanced intermediate is described.

Sir: The talaromycins (A and B), two novel toxins, were isolated by Lynn and co-workers[2] in 1982 from *Talaromyces stripitatas*, a fungus known to grow on animal feed produced from chicken litter, and which renders the feed toxic to mammals. Structural assignments (**1** and **2**, respectively) were based in large part on two-dimensional



Talaromycin A
(1)

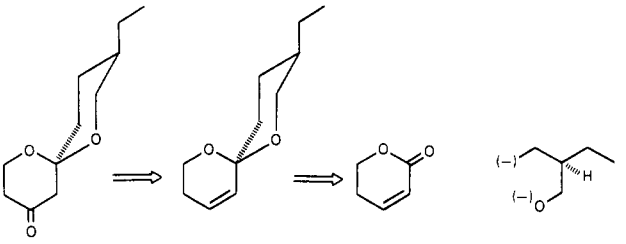


Talaromycin B
(2)

proton NMR correlation spectra (2D COSY) of a 1:1 mixture.[2] Tentative assignment of absolute configuration rests on application of the ORD-benzoate sector rule to the dibenzoate of talaromycin A (**1**).[2,3] Of particular interest from a synthetic point of view was the quantitative conversion of talaromycin A to B upon treatment with acid.[2,4]

Our interest in the talaromycins as synthetic targets stemmed directly from the spiroketal moiety central to the milbemycin–avermectin family of macrolide antibiotics.[5] In this communication we record the first enantioselective total synthesis of both (–)-talaromycin A and B. We note in advance that this work confirms the structure of talaromycin A as well as the absolute configurations of both isomers. Furthermore, the synthesis is economic (i.e., short, 10 steps), affording both talaromycins A and B from a common advanced intermediate.

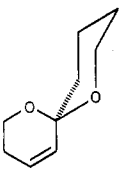
Scheme I



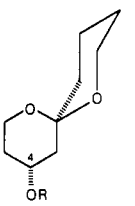
3 4 5 6

At the outset, we set as overall goal the development of a synthetic strategy that would not only lead to the talaromycins but would also provide access to a number of simple structural derivatives for biological testing. Our synthetic analysis is illustrated in Scheme I. Removal of the hydroxymethyl substituent leads to the first synthetic subtarget (**3**). We anticipated that regioselective hydroxymethylation would yield a mixture of epimers, which, after carbonyl reduction, would lead to both talaromycin A and B. In this regard, Lynn[2] reported that while the talaromycins are not readily separable, esterification with phenylboronic acid yields a seperable mixture. Basic hydrolysis then gives the talaromycins in pure form.

Continuing with this analysis, ketone **3** was anticipated to derive from regioselective hydration of olefin **4**, the latter envisioned to arise via addition of dianion **6** or its equivalent to lactone **5**. To examine the feasibility of this strategy, in particular, construction of olefin **4** and its conversion to ketone **5**, we explored the synthesis of the norethyl derivative **7**.[6] Toward this end, addition of the



7



8: R = $CH_2CH{=}CH_2$
9: R = H

Normant[7] Grignard derived from 4-chloro-1-butanol to lactone **5**[8] gave, after acidic workup, spiroketal **7** albeit in poor yield (ca. 15%). After considerable experimentation a modest improvement was obtained when the Grignard derived from the ethoxyethyl ether of 4-bromo-1-butanol was employed. The yield in this case, while still modest (ca. 35%), allowed rapid construction of the spiropyrano skeleton.

Turning next to hydration of the C(3,4) olefinic bond, reaction of **7** with allyl alcohol (TsOH) afforded **8**[9,10] in near

(1) Camille and Henry Dreyfus Teacher–Scholar, 1978–1983; National Institutes of Health (National Cancer Institute) Career Development Award, 1980–1985.

(2) Lynn, D. G.; Phillips, N. J.; Hutton, W. C.; Shabanowitz, J.; Fennel, D. I.; Cole, R. J. *J. Am. Chem. Soc.* **1982**, *104*, 7319.

(3) Nakanishi, K.; Harada, N. "Circular Dichroic Spectroscopy-Exiton Coupling in Organic Stereochemistry"; University Science Books: Mill Valley, CA, 1983; Chapter 3.

(4) This observation led to an elegant synthesis of talaromycin B by Schreiber; see: Schreiber, S. L.; Sommer, T. J. *Tetrahedron Lett.* **1983**, *24*, 4781. After completion of our work two additional syntheses of talaromycin B appeared. See: Kocienski, P.; Yeates, C. *J. Chem. Soc., Chem. Commun.* **1984**, 151. Kozikowski, A. P.; Scripko, J. G. *J. Am. Chem. Soc.* **1984**, *106*, 343.

(5) (a) Milbemycin: Mishima, H.; Kurabayashi, M.; Tamura, C. *Tetrahedrn Lett.* **1975**, 711. Also see: Takiguchi, Y.; Mishima, H.; Okuda, M.; Terao, M.; Aoki, A.; Fukuda, R. *J. Antibiotics* **1980**, *33*, 1120. (b) Avermectin: Albers-Schonberg, G.; Arison, B. H.; Chabala, J. C.; Douglas, A. W.; Eskola, P.; Fisher, M. H.; Lusi, A.; Mrozik, H.; Smith, J. L.; Tolman, R. L. *J. Am. Chem. Soc.* **1981**, *103*, 4216. Springer, J. P.; Arison, B. H.; Hirshfield, J. M.; Hoogsteen, K. *Ibid.* **1981**, *103*, 4221. (c) Milbemycin synthesis: Smith, A. B., III; Schow, S. R.; Bloom, J. D.; Thompson, A. S.; Winzenberg, K. N. *J. Am. Chem. Soc.* **1982**, *104*, 4015. Williams, D. R.; Barner, B. A.; Nishitani, K.; Phillips, J. G. *Ibid.* **1982**, *104*, 4708.

(6) Construction of the norethyl and other closely related derivatives of the talaromycins for biological testing is underway in our laboratory.

(7) Cahiez, G.; Alexakis, A.; Normant, J. F. *Tetrahedron Lett.* **1978**, 3013.

(8) This lactone is readily available from vinyl acetic acid and paraformaldehyde; see: Nakagawa, M.; Saegusa, J.; Tonozuka, M.; Obi, M.; Kiuchi, M.; Hino, T.; Ban, Y. *Org. Synth.* **1976**, *56*, 49.

(9) The regioselective introduction of oxygen was anticipated on the basis of work in the avermectin area, see: Mrozik, H.; Eskola, P.; Arison, B. H.; Albers-Schonberg, G.; Fisher, M. H. *J. Org. Chem.* **1982**, *47*, 489. Also see, ref 11.

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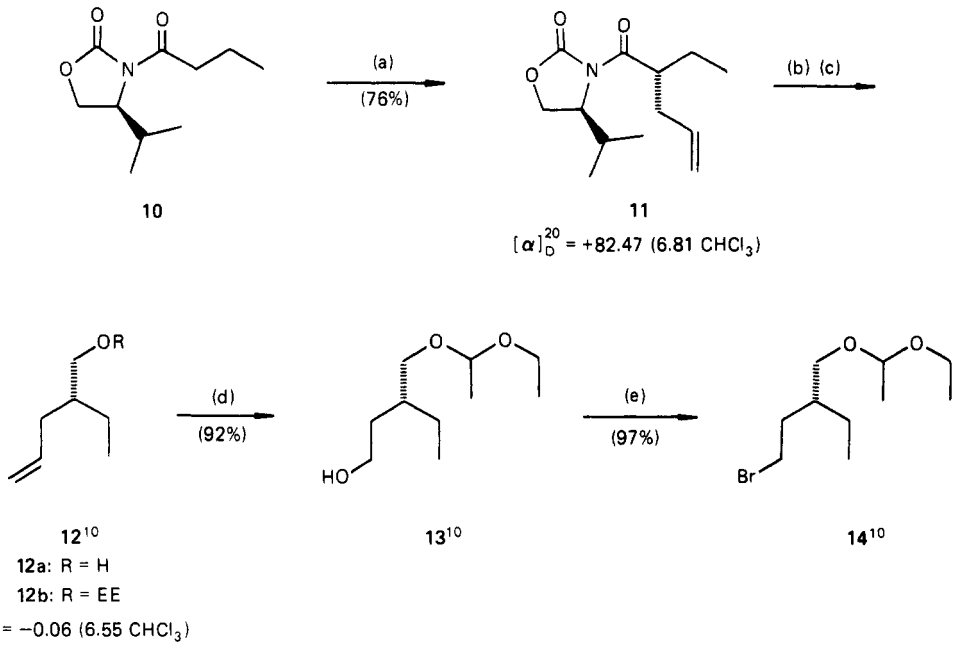
Scheme II[a]



10

11

$[\alpha]_D^{20}$ = +82.47 (6.81 $CHCl_3$)

12[10]

12a: R = H

12b: R = EE

$[\alpha]_D^{20}$ = −0.06 (6.55 $CHCl_3$)

13[10]

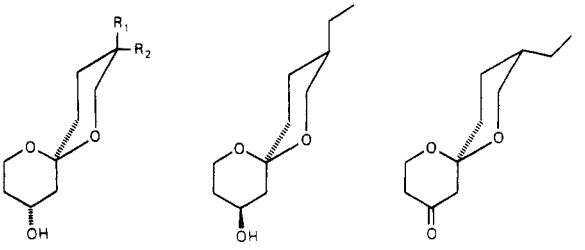
14[10]

[a] (a) $LiN(SiMe_3)_2$/−78 °C, CH_2=$CHCH_2Br$/−78 to 0 °C; (b) 1.1 equiv of LAH/Et_2O/0 °C; (c) EtOCH=CH_2/*p*-TsOH/CH_2Cl_2/0 °C, 15 min; (d) O_3/MeOH/CH_2Cl_2/K_2HPO_4/−78 °C, Me_2S, $NaBH_4$/0 °C; (e) CBr_4/Ph_3P/CH_2Cl_2/pyridine/0 °C, 2 h.

quantitative yield.[11] The facility and regiochemistry of this addition process is explicable in terms of an acid-catalyzed "Michael like" addition to the open oxonium form of **7**, followed by reketalization. Reductive removal of the allyl group (Li/liquid NH_3) afforded **9**, a known compound;[11] the yield was 80%. Structure **9** was varified by comparison of the ^1H NMR spectrum with that kindly provided by Professor Baker (Southampton).[12] Alternatively, **9** could be obtained directly from **7** by treatment with HCl/H_2O/THF (1:5:20); in this case the yield was 85%. In practice, olefin **7** is no longer isolated; rather the Grignard reaction mixture is simply treated with HCl/H_2O/THF (1:5:20) and **9** isolated directly.

Convinced of the overall viability of the synthetic strategy, bromide **14**[10] with proper absolute stereochemistry (i.e., *R*) for the talaromycins was prepared in five steps (40% overall yield) from oxazolidone **10**,[13] employing the Evans[14] asymmetric induction procedure (see Scheme II).

Reaction of the Grignard reagent derived from bromide **14** with lactone **5** followed by the same acidic hydration protocol led, somewhat surprisingly,[15] to a 2:2:1 mixture (NMR) of alcohols **15a**, **15b**, and **16**. For our purposes



15

15a: R_1 = Et, R_2 = H

15b: R_1 = H, R_2 = Et

16

17

this mixture is of little consequence in that oxidation with Jones reagent affords a 8.5:1 mixture of spiro ketones **3**[10b] and **17**.[10] Apparently, Jones reagent[16] is sufficiently acidic to equilibrate the ketone mixture via an acyclic intermediate to provide the thermodynamic product ratio. Support for this conjecture derives from the fact that less acidic oxidation reagents (e.g., PCC[17] and Collins[18] reagent) afford the same ketones, albeit in a ratio of 1:1. Subsequent treatment of this mixture with mild acid [HCl/H_2O/THF (1:5:20)] leads in quantitative yield to the identical 8.5:1 ratio obtained via Jones oxidation.

(10) (a) All new compounds gave 250-MHz ^1H NMR, IR, and high-resolution mass spectra in accord with the structures given. (b) This compound also gave satisfactory C, H combustion analysis. All yields recorded here are based upon isolated material which was ≥97% pure. The NMR and IR spectra of representative intermediates are given below. **3**: IR ($CHCl_3$) 2975 (b), 1725 (s), 1250 (b), 1055 (m); NMR (250 MHz, $CDCl_3$) δ 4.05–3.80 (m, 2 H), 3.64–3.50 (m, 1 H), 3.24–3.15 (app t, *J* = 11 Hz, 1 H), 2.58–2.47 (ddd, *J* = 14.6 Hz, 11.9 Hz, 8.4 Hz, 1 H), 2.40 (br s, 2 H), 2.34–2.25 (br d, *J* = 14.5 Hz, 1 H), 1.92–1.84 (m, 1 H), 1.75–1.30 (m, 4 H), 1.25–1.05 (m, 2 H), 0.86 (t, *J* = 7 Hz, 3 H). **7**: IR ($CHCl_3$) 3025 (w), 2990 (s), 2940 (b), 2870 (s), 995 (b), 890 (s); NMR (250 MHz, $CDCl_3$) δ 5.94 (app t, *J* = 10 Hz, 1 H), 5.62 (d, *J* = 10.0 Hz, 1 H), 3.98–3.48 (m, 4 H), 2.40–2.14 (m, 1 H), 1.97–1.38 (m, 7 H). **18a**: IR ($CHCl_3$) 3650–3350 (b), 2970 (b), 1720 (s), 1238 (b), 1090–1040 (b); NMR (250 MHz, $CDCl_3$) δ 4.02 (dd, *J* = 11.6 Hz, 4.1 Hz, 1 H), 3.89–3.82 (m, 3 H), 3.56 (br d, *J* = 11.0 Hz, 1 H), 3.22 (app t, *J* = 10.8 Hz, 1 H), 2.55 (m, 1 H), 2.55 (d, *J* = 15.2 Hz, 1 H), 2.42 (d, *J* = 15.2 Hz, 1 H), 2.00 (br s, 1 H), 1.84 (br d, *J* = 11 Hz, 1 H), 1.75–1.35 (m, 4 H), 1.25–1.05 (m, 2 H), 0.85 (t, *J* = 7.3 Hz, 3 H). **18b**: IR ($CHCl_3$) 3650–3450 (b), 2970 (b), 1718 (s), 1230 (m), 1090 (s), 1050 (s); NMR (250 MHz, $CDCl_3$) δ 3.96 (dd, *J* = 10.8 Hz, 7.4 Hz, 1 H), 3.80–3.64 (m, 3 H), 3.54 (br d, *J* = 11.0 Hz, 1 H), 3.17 (app t, *J* = 10.8 Hz, 1 H), 2.70 (m, 1 H), 2.48 (d, *J* = 14.0 Hz, 1 H), 2.42 (m, 1 H), 2.38 (d, *J* = 14.0 Hz, 1 H), 1.87 (br d, *J* = 10 Hz, 1 H), 1.75–1.30 (m, 4 H), 1.25–1.05 (m, 2 H), 0.85 (t, *J* = 7.3 Hz, 3 H).

(11) (a) Baker, R.; Herbert, R. H.; Parton, A. H. *J. Chem. Soc., Chem. Commun.* **1982**, 601.

(12) We thank Professor Raymond Baker for supplying us with a 90-MHz NMR spectrum of **9**.

(13) Evans, D. A.; Ennis, M. D.; Mathre, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 1737.

(14) Evans, D. A.; Nelson, J. V.; Taber, T. R. *Top. Stereochem.* **1982**, *13*, 1.

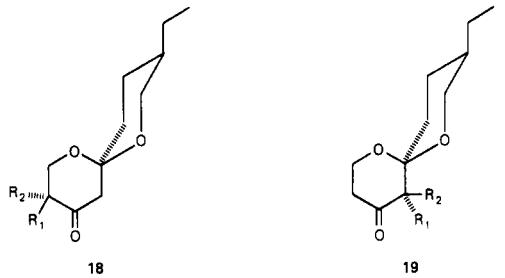
(15) At the onset it was anticipated that addition of water to this olefin would be a reversible process and would lead to a thermodynamic mixture of alcohols **15a** and **16**. The fact that alcohol **15b** was also isolated (even after prolonged reaction times) indicates that hydration of this olefin is not reversible under these conditions.

(16) Bowden, K.; Heilbron, I. M.; Jones, E. R. H.; Weedon, B. C. L. *J. Chem. Soc.* **1946**, 39. Also see: Fieser, L. F.; Fieser, M. "Reagents for Organic Synthesis"; Wiley: New York, 1967; Vol. 1, pp 142–144.

(17) Corey, E. J.; Suggs, W. J. *Tetrahedron Lett.* **1975**, 2647.

(18) Collins, J. C.; Hess, W. W.; Frank, F. J. *Tetrahedron Lett.* **1968**, 3363.

With ample quantities of subtarget **3** in hand, there remained only introduction of the hydroxymethyl substituent and reduction of the carbonyl to complete a synthesis of the talaromycins. While conceptually straightforward, the regio- and stereochemical problems associated with these operations proved deceptively difficult. Best results for hydroxymethylation were achieved with the lithium enolate of **3**, generated with 1.1 equiv of LiN($SiMe_2Ph$)$_2$[19] [THF, −78 °C], followed by capture at −50 °C with gaseous formaldehyde. Yields were typically in the range of 55–60%, with 25% recovery of starting ketone **3**. Careful separation of the resultant mixture via HPLC [semipreparative, μ-Porasil, hexane–ethyl acetate (3:2)] afforded all four possible isomers (**18a,b** and **19a,b**; 3:1 respectively.) While the axial–equitoral ratio, in both



18 **19**

a: R_1 = H, R_2 = CH_2OH
b: R_1 = CH_2OH, R_2 = H
c: R_1 = H, R_2 = CH_2OBz
d: R_1 = CH_2OBz, R_2 = H

cases 5:1, would allow preparation of talaromycin A and B, respectively, the regiochemical problem was quite troublesome. Unfortunately, all attempts to improve upon this ratio have been unsuccessful.[20]

Undaunted, we turned to reduction of the C(3) carbonyl group. Of the many reagents and protecting groups examined, $Zn(BH_4)_2$ reduction of benzoates **18c**[10] and **18d**[10] provided the best stereoselectivity [i.e., C(4) equatorial hydroxyl]. For example, reduction of **18c** followed with a basic workup (KOH/MeOH) afforded a 4:1 mixture of talaromycin A [α^{20}_D −110.2° (0.83, $CHCl_3$)][21] and its C(4) epimer which were readily seperable by flash chromatography ($CHCl_3$/MeOH, gradient 1–5%). Synthetic (−)-talaromycin A was shown to be identical with natural talaromycin A by careful comparison of the high-field ^{1}H NMR spectral data published by Lynn.[2] To confirm the absolute configuration of natural talaromycin A (and thereby talaromycin B), the dibenzoate of synthetic (−)-**1** was prepared. Both the circular dichromism (i.e., + Cotton effect) and 500-MHz ^{1}H NMR spectra were identical with that obtained from natural talaromycin A.[22] Finally, talaromycin B [α^{20}_D −84.1° (0.46, $CHCl_3$)][21] was available either from **18d** [$Zn(BH_4)_2$; KOH workup] or by treatment of (−)-talaromycin A (**1**) with HCl/H_2O/THF (1:5:20).

In summary, the first enantioselective synthesis of talaromycin A and B has been achieved from a common advanced intermediate. The synthetic route is economic (i.e., short), serves both to confirm the structure of talaromycin A as well as the absolute configuration of talaromycin A and B, and is amenable to analogue synthesis.[23]

Acknowledgment. It is a pleasure to acknowledge the support of this investigation by the National Institutes of Health (General Medical Sciences) through Grant No. 29028. In addition, we thank Drs. G. Furst and T. Terwilliger of the University of Pennsylvania Spectroscopic Facilities for aid in obtaining the high-field NMR and MS spectral data, respectively.

(19) Masamune, S.; Ellingboe, J. W.; Choy, W. *J. Am. Chem. Soc.* **1982**, *104*, 5526.

(20) A variety of amide bases were employed to generate the enolate(s) of ketone **3**. Subsequent capture with Me_3SiCl afforded the corresponding enol silyl ethers; regioisomeric ratios were then determined by NMR employing the vinyl resonance as probe. LDA and LiN[$SiPhMe_2$]$_2$ were found to give the best selectivity. Efforts to improve upon this ratio are currently underway in our laboratory.

(21) The optical rotations of talarmomycins A and B have not been reported previously. Enantiomeric excesses were determined to be 91–93% (Mosher ester method, see: Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 3543.

(22) We thank Professor David Lynn for obtaining the CD spectra and for providing the 500-MHz NMR spectra of talaromycin A and B.

(23) After completing this manuscript, we learned that Professor Schreiber (Yale) has completed a total synthesis of (±)-talaromycin A; private communication from Professor Schreiber.

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