

Total Syntheses of (+)-Acutiphycin and (+)-*trans*-20,21-Didehydroacutiphycin

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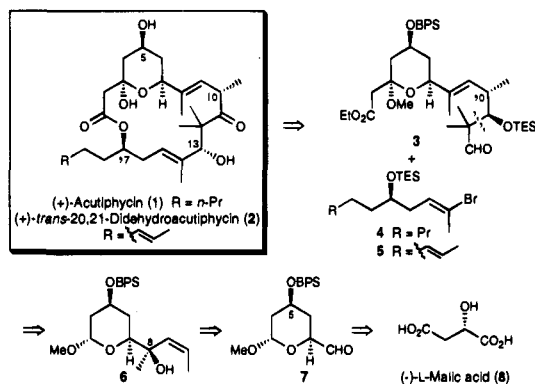
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In 1984, Moore and co-workers reported the isolation and characterization of the architecturally novel macrolides (+)-acutiphycin (**1**) and (+)-*trans*-20,21-didehydroacutiphycin (**2**).¹ Both compounds exhibited significant antineoplastic activity *in vivo* against murine Lewis lung carcinoma and cytotoxicity against the KB and NIH/3T3 cell lines.¹ The natural source, the blue-green alga *Osillatoria acutissima*, no longer produces these metabolites;² further biological evaluation as well as structure confirmation therefore mandated synthesis. Our longstanding interest in the construction of biologically active hemi- and spiroketals led us to undertake the first total syntheses of **1** and **2**. Challenging features of the targets included the chemical sensitivity of the β -carbalkoxy hemiketal moiety and the C(10) stereocenter as well as the very considerable steric congestion of the 16-membered ring.

Retrosynthetically, we envisioned cleavage of the macrocyclic lactones followed by disconnection between C(13) and C(14), leading to common advanced aldehyde **3** and vinyl anion precursors **4** and **5** (Scheme 1). Aldehyde **3** would arise via an

Scheme 1



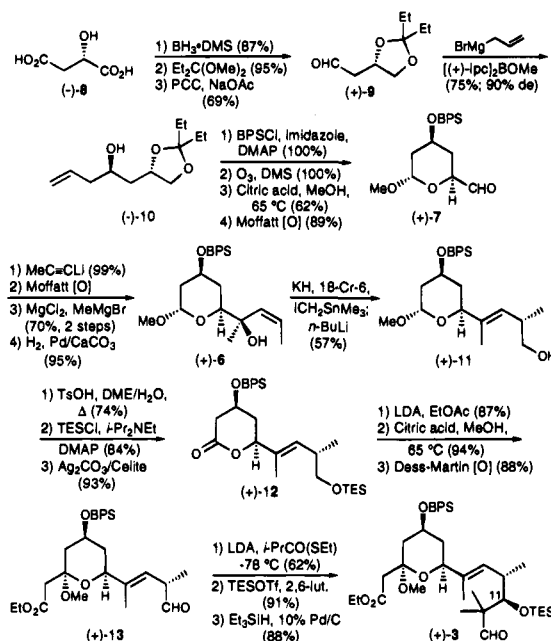
acyclic stereocontrol strategy beginning with L-malic acid (**8**). Critical transformations would include a Brown asymmetric allylboration^{3a} to set C(5), chelation-controlled introduction of the C(8) methyl group^{3b} and Still [2,3]-sigmatropic rearrangement^{3c} to install both the C(10) center and the 8,9-(*E*)-trisubstituted olefin, Cram enolate addition to generate C(11),^{3d} and chemoselective thioester reduction in the presence of the ethyl ester.

As our point of departure, hydroboration⁴ of (-)-L-malic acid (**8**) and triol protection⁵ as a ketal afforded almost exclusively

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(3) (a) Brown, H. C.; Jadhav, P. K. *J. Am. Chem. Soc.* **1983**, *105*, 2092.
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the thermodynamically preferred⁶ dioxolane (>10:1; Scheme 2). After oxidation to (+)-**9**^{7a} with buffered PCC,⁸ addition of Brown's (+)-allyl(diisopinocampheyl)borane^{3a} gave homoallylic alcohol (-)-**10**⁷ with excellent diastereoselectivity (90% de). Silylation with *tert*-butyldiphenylsilyl chloride (BPSCl), reductive ozonolysis, and ketal methanolysis with concomitant cyclization (citric acid, MeOH, reflux, 18 h) furnished the requisite methyl pyranoside as a chromatographically separable 3:1 mixture of α and β anomers. Moffatt oxidation⁹ of the α anomer then produced aldehyde (+)-**7**.^{7a}

Scheme 2

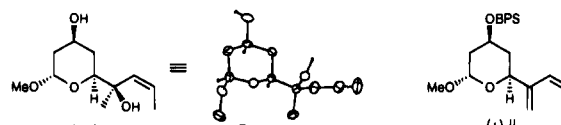


Addition of 1-lithio-1-propyne to **7** afforded a mixture of alcohols which was submitted to a second Moffatt procedure (Scheme 2). Chelation-controlled addition of methylmagnesium bromide and semihydrogenation with Lindlar's catalyst then yielded tertiary allylic alcohol (+)-**6**,⁷ the relative stereochemistry was verified by X-ray analysis of a crystalline derivative.^{10a} The ether substrate for the [2,3]-sigmatropic rearrangement was prepared *in situ* by deprotonation of **6** with KH and 18-crown-6 in THF and alkylation with $\text{Me}_3\text{SnCH}_2\text{I}$.¹¹ The reaction mixture was immediately cooled to -78 °C and treated with *n*-BuLi, affording the rearranged alcohol (+)-**11**⁷ as the major product.^{10b} Following acidic hydrolysis and selective silylation of the primary alcohol with triethylsilyl chloride (TESCl), the resultant lactol was oxidized to lactone (+)-**12**.^{7,12} Addition of the lithium enolate of ethyl acetate to the lactone carbonyl,¹³ methanolysis

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(7) (a) The structure assigned to each new compound was in accord with its infrared, 500-MHz ¹H NMR and 125-MHz ¹³C NMR spectra, as well as appropriate parent ion identification by high-resolution mass spectrometry. (b) In addition, an analytical sample of this compound, obtained by recrystallization or liquid chromatography, gave satisfactory combustion analysis (within 0.4%).

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(10) (a) Treatment of (+)-**6** with TBAF provided the crystalline diol (+)-**11**^a (mp 80–82 °C). (b) Diene (+)-**11**^b was also obtained (41% yield).

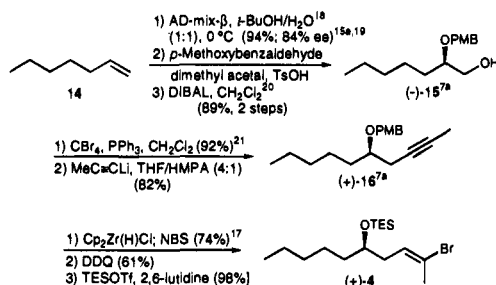


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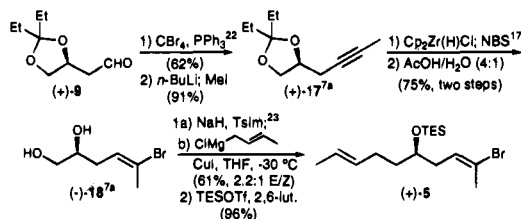
of the TES group with concomitant formation of the mixed methyl ketal, and Dess–Martin oxidation¹⁴ furnished aldehyde (+)-**13**.^{7a} Reaction with the lithium enolate of ethyl isobutane-thioate provided a separable 3.4:1 mixture of alcohols; as predicted by the Cram model^{3d} and confirmed via the Mosher ester method.¹⁵ Finally, silylation of the hydroxyl and chemoselective reduction¹⁶ of the thiol ester (triethylsilane, catalytic 10% Pd/C) gave aldehyde (+)-**3**.^{7a}

The concise preparations of vinyl bromides (+)-**4**^{7a} and (+)-**5**,^{7a} outlined in Schemes 3 and 4, exploited a regiocontrolled, highly stereoselective hydrozirconation–bromination¹⁷ procedure in the key step (*E/Z* 16.4:1 and 16:1, respectively). Aldehyde (+)-**3** was then coupled with vinyl bromides (+)-**4** or (+)-**5** via the derived vinyl Grignard reagents (Scheme 5), generating 1:1 mixtures of epimeric alcohols, which furnished enones (+)-**19a**^{7a} and (+)-**19b**^{7a} upon Dess–Martin oxidation.¹⁴ In each sequence, removal of the TES groups and directed reduction of the β -hydroxy ketone with tetramethylammonium triacetoxyborohydride²⁴ gave the desired diol with very high diastereoselectivity (92% de).²⁵ Ester saponification then produced seco acids (+)-**20a**^{7a} and (+)-**20b**,^{7a} substrates for the critical macrolactonization.

Scheme 3



Scheme 4



We investigated several cyclization methods,²⁶ among which the Yamaguchi protocol^{26a} proved superior. Although these

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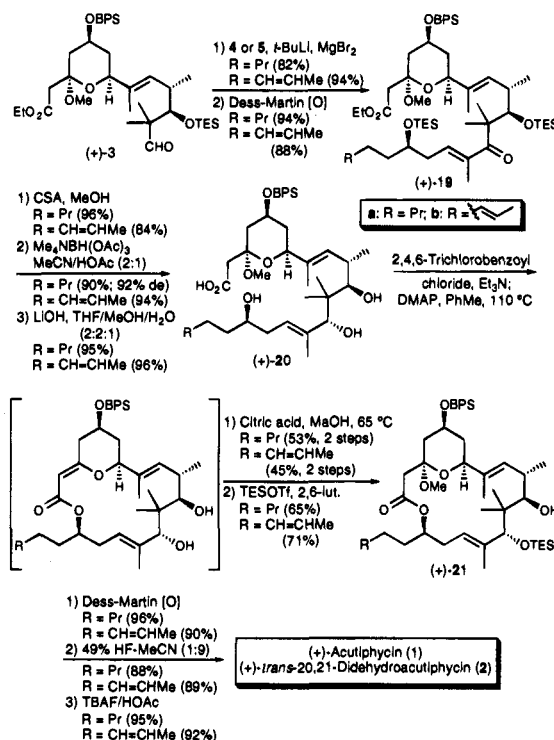
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(25) The C(13) stereogenicity in both cases was established via ¹³C NMR analysis of the derived 1,3-acetonides; see: (a) Rychnovsky, S. D.; Skalityzky, D. *J. Tetrahedron Lett.* **1990**, *31*, 945. (b) Evans, D. A.; Rieger, D. L.; Gage, J. R. *Tetrahedron Lett.* **1990**, *31*, 7099.

Scheme 5



conditions also led to elimination of the C(3) methoxy group, the latter functionality could be reinstated simply by heating the macrolide in methanolic citric acid (0.5 mM) for 3 days. Selective silylation of the C(13) hydroxyl then generated alcohols (+)-**21a**^{7a} and (+)-**21b**.^{7a} Dess–Martin oxidation¹⁴ produced the corresponding ketones without observable epimerization at C(10) or migration of the C(8,9) double bond. Exposure to 49% HF in CH₃CN removed the TES group and also hydrolyzed the methyl pyranoside. Completion of the synthetic venture entailed removal of the BPS moiety [TBAF buffered with acetic acid (1:1)]²⁷ to afford (+)-acutiphycin (**1**)^{7a} and (+)-*trans*-20,21-didehydroacutiphycin (**2**),^{7a} identical with the natural materials in all respects (500-MHz ¹H and 125-MHz ¹³C NMR, IR, HRMS, mp, mmp, optical rotation, and TLC in four solvent systems).²⁸

The first total syntheses of (+)-acutiphycin (**1**) and (+)-*trans*-20,21-didehydroacutiphycin (**2**) confirm the structures and absolute stereochemistries originally assigned by Moore. We anticipate that the successful strategy can be extended to provide a series of novel analogs, as well as material for further biological evaluation of **1** and **2**.

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Supporting Information Available: Spectroscopic data for **1–7**, **9–13**, **15–21**, **i**, and **ii** as well as selected experimental procedures (14 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

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