CHPh, 83413-35-8; (E)-HOCH2CH(CH=CH2)CH=CHPh, 83413-27-8; (E,E)-BOCN(H)-o-C₆H₄-CH=CHCH₂CH=CHCH₂OH, 114467-60-6; (E)-BOCN(H)-o-C₆H₄-CH=CHCH(CH=CH₂)CH₂OH, 114467-61-7; (E,E)-HOCH2CH=CHCH2CH=CHTMS, 114467-62-8; (*E*)-HOCH₂CH(CH=CH₂)CH=CHTMS, 114467-63-9; (*E*)-PhCH-(OH)CH=CHCH₂Ph, 72486-03-4; (E)-PhCH(OH)CH= CHCH₂CH=CH₂, 114467-64-0; PhCH(OH)CH(CH=CH₂), 10544-99-7; (*E*,*E*)-PhCH(OH)CH=CHCH₂CH=CHPh, 114467-65-1; (*E*)-PhCH(CH=CH₂)CH=CHCH₂OH, 114467-66-2; (*E*)-PhCH= CHCH(CH=CH₂)CH₂OH, 83413-27-8; (CH₃CN)₂PdCl₂, 14592-56-4; (4-tert-butylcyclohexenyl)trimethylstannane, 102073-66-5; (E)-4-(1,1dimethylethyl)-1-(2-methylbut-2-en-1-ol-4-yl)cyclohexene, 114467-52-6; trans-1-hydroxy-4-phenylcyclohexane, 5769-13-1.

Total Synthesis of (+)-18-Deoxynargenicin A₁

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In 1980, workers at Pfizer and Upjohn reported the first examples of a new structural class of antibiotics, the nargenicins. Nargenicin A1 (1), isolated from Norcardia argentinensis Huang sp. nov., exhibits in vivo activity against gram-positive bacteria, including drug-resistant strains.¹ Nodusmicin (2), a related antibiotic from Saccharopolyspora hirsuta, has been characterized by X-ray crystallography and the relationship to 1 demonstrated by synthetic interconversion.^{2,3} Other nargenicins,⁴⁻⁶ including the 18-deoxy congener 3,4 have now been isolated. The unique structure and biological activity of these macrolides have fostered considerable interest in their pharmacology⁷ and biosynthesis,^{3,8} and several groups have described preliminary synthetic studies.9,10 We now report the first total synthesis of a naturally occurring nargenicin macrolide, (+)-18-deoxynargenicin A₁ (3).

Previous work in our laboratories has resulted in an efficient, stereocontrolled route to the 11-oxatricyclo[4.4.1.0^{2,7}]undecene nucleus characteristic of the nargenicins.⁹ Our entry to this novel ring system is based on the addition of nucleophilic reagents to ketone 4 (available in 7 steps from benzoquinone);^{9a} addition of the resulting alkoxide to the C_8 - C_9 epoxide (nargenicin numbering system) establishes the C_8-C_{13} ether bridge (Figure 1). We reasoned that this approach could be extended to the synthesis of an advanced intermediate incorporating the key structural and stereochemical elements of 3, by addition of a vinyl lithium reagent

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(5) (a) Tone, J.; Shibakawa, R.; Maeda, H.; Yamauchi, Y.; Niki, K.; Saito, M.; Tsukuda, K.; Whipple, E. B.; Watts, P. C.; Moppett, C. E.; Jefferson, M. T.; Huang, L. H.; Cullen, W. P.; Celmer, W. D. Abstract No. 62 from the 20th Interscience Conference of Antimicrobial Agents and Chemotherapy, September 22, 1980. (b) Celmer, W. D.; Cullen, W. P.; Shibakawa, R.; Tone, J. (to Pfizer Inc., New York) U.S. Patent 4,435,747. See Chem. Abstr. 1984, 101, 53332

101, 53332.
(6) The structure of coloradocin, a bis-macrolide related to the nargenicins, has been reported: Rasmussen, R. R.; Scherr, M. H.; Whittern, D. N.; Buko, B. N.; McAlpine, J. B. J. Antibiot. 1987, 40, 1383.
(7) (a) Magerlein, B. J.; Miszak, S. A. J. Antibiot. 1982, 35, 111. (b) Magerlein, B. J. Abstract No. Medi 72 from the 182nd National Meeting of the American Chemical Society, August 23-28, 1981.
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Steliou, K.; Poupart, M.-A. J. Am. Chem. Soc. 1983, 105, 7130.

$$\label{eq:Rsecond} \begin{split} R_s &= 2\text{-carboxypyrrole} \quad R_{2^m} OH \quad \text{nargencin} \; A_1, \\ R_s &= H, \; R_{2^m} OH, \; \text{nodusmicin} \\ R_1 &= 2\text{-carboxypyrrole} \; , \; R_{2^m} \; H \; \; 18 \; \text{decxynargencin} \; A_1, \end{split}$$

Figure 1.



Figure 2.

representing the C_{14} - C_{19} fragment of the nargenicin macrolide system to enone 4. Iodide (+)-5a, possessing the functionality and stereochemistry of the required C_{14} - C_{19} subunit, has been reported by Corey in the context of a total synthesis of erythronolide B.¹¹ For the present application, we required the methoxymethyl protected derivative (+)-5b, readily available from (+)-crotyl epoxide¹² using a modification of the Corey scheme.

Addition of the vinyl lithium reagent derived from (+)-5b (2 equiv of t-BuLi, Et₂O, -78 °C) to racemic enone 4 gave the expected mixture of diastereomeric products 6, which were transformed directly to the methoxymethyl-protected derivatives 7 (Scheme I).¹³ While 7a and 7b were readily separated by flash chromatography, we were unable to unambiguously identify the desired diastereomer by spectroscopic methods; consequently, each diastereomer was independently carried through the next synthetic sequence (for clarity, only transformations of diastereomer 7a are shown). Allylic oxidation of 7 with 3,5-dimethylpyrazole-CrO₃ complex¹⁴ (CH₂Cl₂, -20 °C) afforded enone 8 in modest yield. Introduction of the C_1 - C_3 subunit of the nargenicins was accomplished by addition of the mixed cuprate reagent 9, followed by immediate trapping of the resulting enolate as the enol phosphodiamidate and dissolving metal reduction¹⁵ to afford 10. The stereochemistry of cuprate addition to 8 is consistent with our observations in related model systems^{9b} and is presumably a consequence of initial coordination of the cuprate reagent to the oxygen of the ether bridge. That we had introduced the C_1-C_3 subunit with the desired relative stereochemistry was demonstrated by selective deprotection of 10 and Jones oxidation of the resulting primary alcohol to afford the crystalline acids 11. X-ray crystallography of one of the diastereomeric acids revealed this material to be 11b,¹⁶ allowing us to confine our final synthetic transformations to the "natural" diastereomer 11a.

Introduction of the C_2 methoxyl was accomplished by enolate oxidation¹⁷ of ester 12^{-} (LDA, MoO₅-HMPA-pyridine) and

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Scheme I^a

OMON OMOM d,e 39% 20 EEC ÓNON NOMO MOM <u>6a;</u> R= H <u>7a;</u> R= CH₂OCH₃ 82 <u>10a</u> f,ç 5a; R= t-BuMe,SI омом 5b; R= CH2OCH3 c-g 80.0 омом **ÖNOM** OMOM MOM 11a; R= H 12; R= CH, 115 65; R= H 75; R= CH2OCH3 MOM= -CH2OCH3 EE= -CH(CH3)OCH2CH3 I, j 50% 20% RO.C 32% <u>15a</u> $\begin{array}{c} \underline{13} \hspace{0.1 cm} ; \hspace{0.1 cm} \mathsf{R} = \hspace{0.1 cm} \mathsf{Me}, \hspace{0.1 cm} \mathsf{R}_1 = \hspace{0.1 cm} \mathsf{MOM} \\ \underline{14} \hspace{0.1 cm} ; \hspace{0.1 cm} \mathsf{R} = \hspace{0.1 cm} \mathsf{R}_1 = \hspace{0.1 cm} \mathsf{H} \end{array} \hspace{0.1 cm} \left. \begin{array}{c} a \hspace{0.1 cm} ; \hspace{0.1 cm} \mathsf{R}_2 = \alpha \hspace{0.1 cm} \cdot \hspace{0.1 cm} \mathsf{OMe} \\ b \hspace{0.1 cm} ; \hspace{0.1 cm} \mathsf{R}_2 = \beta \hspace{0.1 cm} \cdot \hspace{0.1 cm} \mathsf{OMe} \end{array} \right. \end{array} \right.$ 3; 18-deoxynargenicin A,

^a Reagents: a) 2 eq. t-BuLi, (±)-4, -78-0°C; b) MeOCH₂Cl, EtN(i-Pr)₂, CH₂Cl₂, 25°C; c) CrO₃-3,5-dimethylpyrazole, CH₂Cl₂, -20°C; d) $\stackrel{\text{EEO}}{9}$, THF, -78°, then (Me₂N)₂POCl; e) Li, NH₃, THF, t-BuOH, -30-0°C; f) 0.01 M HCl, H₂O-THF, 25°C; g) CrO₃, H₂O-acetone, -20°C; h) CH₂N₂, Et₂O, 0°C; i) LDA, MoO₅-pyridine-HMPA, THF, -78°C; j) Ag₂O, CH₃I, DMF, 25°C; k) 1 M HCl, H₂O-MeOH, 50°C; l) $\left(\bigcirc N \xrightarrow{S} \right)$, Ph₃P, then xylene, 140°C; m) H_{O₂C} $\bigvee N$, DCC, DMAP, THF, 25°C.

methylation (MeI, Ag₂O, DMF), affording the epimeric esters 13.¹⁸ Hydrolysis under acidic conditions gave the expected mixture of trihydroxy acids 14. The most reliable procedure examined to date for effecting macrolactonization proved to be the thiopyridyl ester procedure of Corey.¹⁹ Surprisingly, slow addition of the thiopyridyl esters derived from acids 14 to refluxing xylene afforded a *single* macrolide product, the desired 15a.²⁰ We attribute the absence of lactonic product arising from 14b to the steric compression between the C₂ and C₁₄ substituents which develops during cyclization of this epimer (Figure 2).²¹ The

identity of lactone 15a was confirmed by $acylation^{7a}$ to give (+)-18-deoxynargenicin A₁ (3), identical with an authentic sample provided by Dr. B. Magerlein.

In summary, we have completed the first total synthesis of a naturally occurring nargenicin macrolide and confirmed the absolute stereochemical assignment for this series.^{3,22} The problem of stereorational introduction of the remote chirality at C_2 , C_{16} , and C_{17} remains unsolved; efforts to address this issue and extend our basic strategy to the 18-hydroxy nargenicins are in progress.

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Supplementary Material Available: Experimental procedures and spectroscopic data for all new compounds and tables listing crystallographic details for 11b, including final atomic coordinates, bond lengths and angles, and anisotropic thermal parameters for non-hydrogen atoms (12 pages). Ordering information is given on any current masthead page.

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⁽¹⁸⁾ The epimeric hydroxy esters obtained from enolate oxidation of 12 could be separated and methylated to give pure samples of 13a and 13b. The former was identical with material obtained from authentic 18-deoxynargenicin by a sequence consisting of hydrolysis, esterification, and exhaustive O-alkylation with CH_3OCH_2CI .

⁽¹⁹⁾ Corey, E. J.; Nicolaou, K. C. J. Am. Chem. Soc. 1974, 96, 5614.
(20) Lactone 15 was obtained in 19% overall yield (38% based on 14a).
Also recovered from the cyclization experiments were starting acids 14 and 10–15% of a mixture of diastereomeric diolides; hydrolysis of this mixture (NaOH, MeOH-H₂O, 25 °C) afforded additional recovered 14.

⁽²¹⁾ The possibility that lactone product from 14b is formed and subsequently undergoes hydrolysis during workup cannot be eliminated at this time. We note that ¹H NMR analysis of 14 recovered from macrocyclization experiments indicates this material to be enriched in acid 14b.

⁽²²⁾ Synthetic 3 exhibited a rotation $[\alpha]_D$ +50.0° (25 °C, CHCl₃); rotation for an authentic sample was $[\alpha]_D$ +72.0°.