CHPh, 83413-35-8; (*E*)-$HOCH_2CH(CH{=}CH_2)CH{=}CHPh$, 83413-27-8; (*E*,*E*)-BOCN(H)-*o*-C_6H_4-$CH{=}CHCH_2CH{=}CHCH_2OH$, 114467-60-6; (*E*)-BOCN(H)-*o*-C_6H_4-$CH{=}CHCH(CH{=}CH_2)CH_2OH$, 114467-61-7; (*E*,*E*)-$HOCH_2CH{=}CHCH_2CH{=}CHTMS$, 114467-62-8; (*E*)-$HOCH_2CH(CH{=}CH_2)CH{=}CHTMS$, 114467-63-9; (*E*)-PhCH(OH)$CH{=}CHCH_2Ph$, 72486-03-4; (*E*)-$PhCH(OH)CH{=}CHCH_2CH{=}CH_2$, 114467-64-0; $PhCH(OH)CH(CH{=}CH_2)_2$, 10544-99-7; (*E*,*E*)-$PhCH(OH)CH{=}CHCH_2CH{=}CHPh$, 114467-65-1; (*E*)-$PhCH(CH{=}CH_2)CH{=}CHCH_2OH$, 114467-66-2; (*E*)-$PhCH{=}CHCH(CH{=}CH_2)CH_2OH$, 83413-27-8; $(CH_3CN)_2PdCl_2$, 14592-56-4; (4-*tert*-butylcyclohexenyl)trimethylstannane, 102073-66-5; (*E*)-4-(1,1-dimethylethyl)-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 A_1

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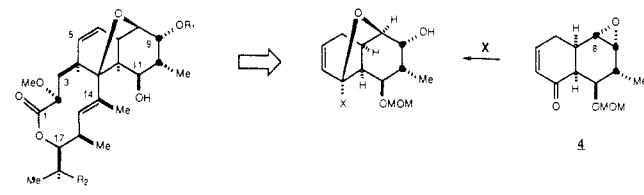
Received December 21, 1987

In 1980, workers at Pfizer and Upjohn reported the first examples of a new structural class of antibiotics, the nargenicins. Nargenicin A_1 (**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 pharmacology[7] 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 A_1 (**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



1 R_1 = 2-carboxypyrrole R_2 = OH nargenicin A_1
2 R_1 = H, R_2 = OH nodusmicin
3 R_1 = 2-carboxypyrrole R_2 = H 18-deoxynargenicin A_1

Figure 1.

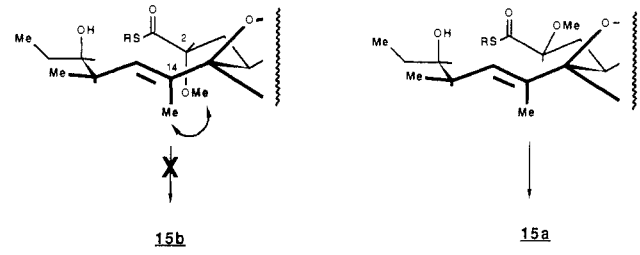


Figure 2.

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 epoxide[12] using a modification of the Corey scheme.

Addition of the vinyl lithium reagent derived from (+)-**5b** (2 equiv of *t*-BuLi, Et_2O, −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–CrO_3 complex[14] (CH_2Cl_2, −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 reduction[15] 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 oxidation[17] of ester **12** (LDA, MoO_5–HMPA–pyridine) and

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(12) Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765. The optical purity of our starting (+)-crotyl epoxide was determined to be 95% by ^1H NMR analysis of the corresponding Mosher ester.
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(16) We are indebted to Professor Clarence Pfluger and Robert Ostrander for obtaining the X-ray crystal structure of this intermediate.

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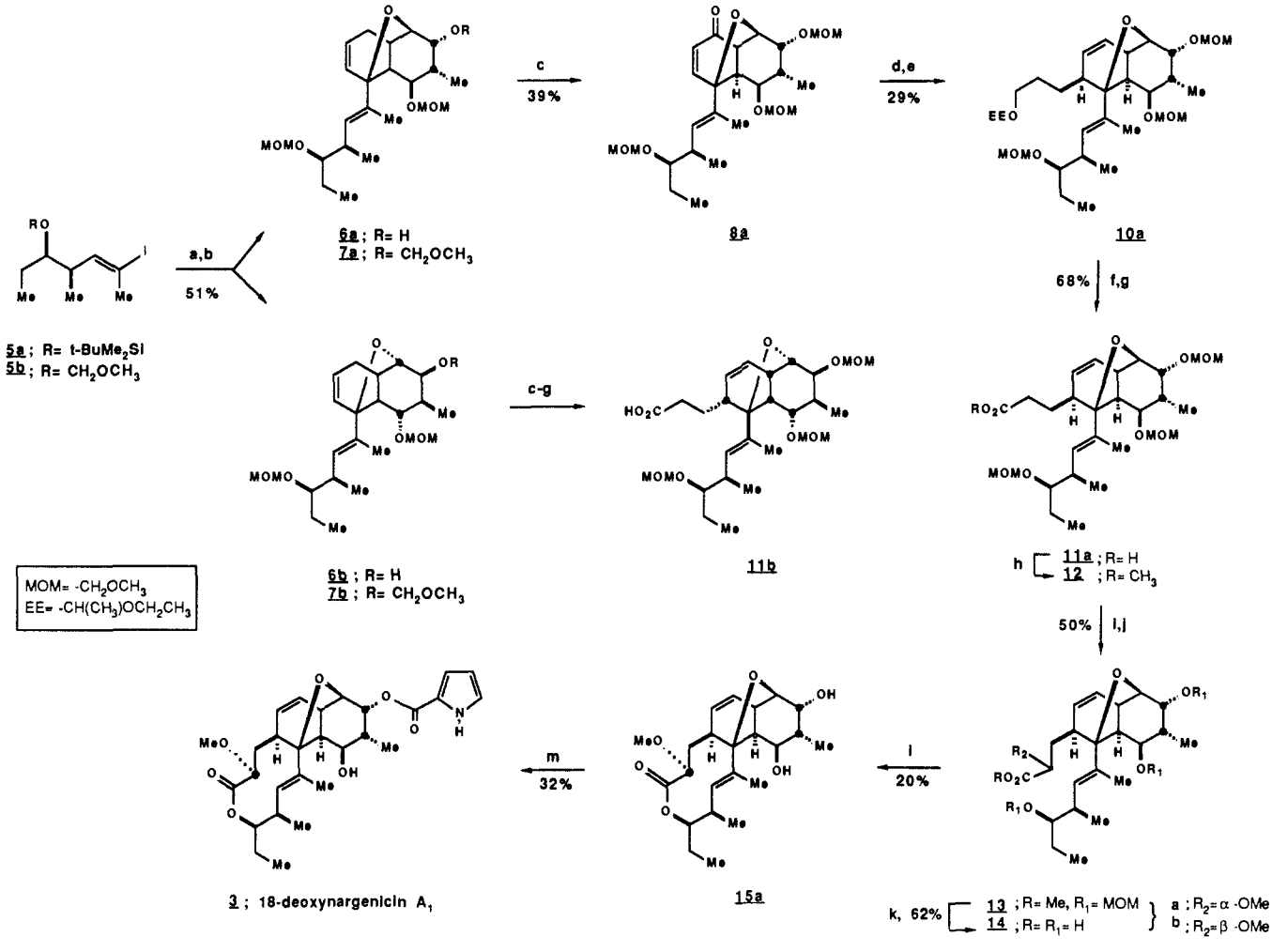
Scheme I[a]



[a] Reagents: a) 2 eq. t-BuLi, (±)-**4**, −78–0°C; b) $MeOCH_2Cl$, $EtN(i\text{-}Pr)_2$, CH_2Cl_2, 25°C; c) CrO_3-3,5-dimethylpyrazole, CH_2Cl_2, −20°C; d) EEO(CH2)4CuCNLi (**9**), THF, −78°, then $(Me_2N)_2POCl$; e) Li, NH_3, THF, t-BuOH, −30–0°C; f) 0.01 M HCl, H_2O-THF, 25°C; g) CrO_3, H_2O-acetone, −20°C; h) CH_2N_2, Et_2O, 0°C; i) LDA, MoO_5-pyridine-HMPA, THF, −78°C; j) Ag_2O, CH_3I, DMF, 25°C; k) 1 M HCl, H_2O-MeOH, 50°C; l) $(2\text{-}C_5H_4NS)_2$, Ph_3P, then xylene, 140°C; m) HO_2C-(2-pyrrole), DCC, DMAP, THF, 25°C.

methylation (MeI, Ag_2O, 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 C_2 and C_{14} 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 A_1 (**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.

Acknowledgment. We gratefully acknowledge the National Institutes of Health (AI-19632) and the Research Corporation for their generous support of this research program. We thank Dr. B. Magerlein of the Upjohn Company for a sample of 18-deoxynargenicin A_1.

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.

(17) (a) Vedejs, E. *J. Am. Chem. Soc.* **1974**, *96*, 5944. (b) Vedejs, E.; Telschow, J. E. *J. Org. Chem.* **1976**, *41*, 740.

(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_2Cl.

(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–H_2O, 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, $CHCl_3$); rotation for an authentic sample was $[\alpha]_D$ +72.0°.