Table III. Enantioselectivity and Rate Constants of Solvolyses[a] of 2-L and 2-D by L-Histidine Dipeptide 1 in Coaggregate Systems Formed by CDEAB (42 molar %) and CHODABA (58 molar %) at Different pH Values

pH	no catalyst 10^3k_{blank}, s^{-1}	10^3k_{mead}(L), s^{-1}	10^3k_{mead}(D), s^{-1}	k_{cat}, $M\ s^{-1}$ 2-L	k_{cat}, $M\ s^{-1}$ 2-D	$k_{cat}(L)/k_{cat}(D)$
7.4	1.9	18.4	2.6	125.0	5.3	23.4
8.0	9.3	26.0	8.4	126.1	−6.8	*b*
9.0	23.0	41.2	14.0	138.0	−68.2	*b*

[a] At 10 °C in 0.02 M Tris-buffer (0.02 M KCl), 3 % (v/v) dioxane–water, [substrate] = 1.00×10^{-5} M, [catalyst] = 1.32×10^{-4} M, [CHODABA] = 6.67×10^{-4} M. [b] Rate retardation for 2D substrate was observed. The rate constants were reproducible within an accuracy of ±3.5%.

the enantioselectivity was low. Particularly noteworthy is the case of the coaggregate system consisting of 50 molar % CHODABA and 50 molar % CDEAB, in which the best enantioselective solvolysis was observed, viz., $k_{cat}(L)/k_{cat}(D)$ = 86.4. Another surfactant ACHODABA, which has an aromatized A ring in the chemical structure, failed to contribute to any significant degree in the enhancement of enantioselectivity.

The above results indicate that to achieve high enantioselective catalysis it is important for the chiral cholesteryl group to be positioned near the polar region of the surfactant where catalytic solvolyses are supposed to take place.

We have also performed the solvolyses of **2**-D or **2**-L by L-histidyl dipeptide **1** in the coaggregate systems of different compositions of CHODABA and CDEAB, as shown in Table II. In response to increased addition of CDEAB, the enantioselectivity was enhanced sharply from 17.4 observed in the presence of vesicle-forming CHODABA alone to 98.2 in the coaggregates containing 42 molar % CDEAB and 58 molar % CHODABA. However, the selectivity decreased with further addition of CDEAB.

When the above solvolyses were carried out in 15 vol % dioxane, the enantioselectivity disappeared completely, presumely due to the complete disarray of the surfactant aggregate system. Electron micrographs show that CHODABA/CDEAB coaggregates actually lose vesicular structures and take on a different morphology, which is not clear on electron micrographs when the coaggregate contains more than 35 molar % CDEAB.

This result is somewhat puzzling to us at the present time. However, it seems to be clear that the kind of morphology of the coaggregate in which high enantioselectivity was observed should be such that the substrate as well as the catalyst can be absorbed into the coaggregate at a proper rate and while the hydrophobic environment is maintained by a certain array formation by the surfactants.

We have further examined the enantioselective solvolysis of **2**-D or **2**-L at different pH values in the above coaggregate system (42 molar % CDEAB/58 molar % CHODABA). The results are presented in Table III.

In Table III it is notable that as pH values of the solvolytic solution are raised, the blank rates increased significantly, probably due to the increased local concentration of hydroxide ion at the periphery of surfactant coaggregates. The catalytic activity (k_{cat}) for the **2**-L remained about same with a slight increase at pH 9.0. The most interesting to observe was, however, that inhibition effect was exhibited by catalyst in the case of the solvolysis of **2**-D at pH 8.0 and 9.0. The values of k_{mead}(D) were actually smaller than those of the blank rates and k_{cat}(D) values were negative.[1c]

We assume that this inhibition by the catalyst is due to the increased portion of imidazole anion,[7] which acts as the counterion of positive ion of surfactant polar heads, thus reducing the local concentration of hydroxide ion at the periphery (Stern layer) of the surfactant coaggregates. This situation should be same in the case of solvolysis of **2**-L. However, the stereochemistry of the intermediate complex (transition state) between catalyst and **2**-L substrate is such that neutral and anionic imidazoles act as attacking nucleophiles, showing yet high k_{cat} values. Obviously, this is not occurring in the case of solvolysis of **2**-D.

The detailed mechanism and stereochemical pictures are not yet clear to us at the present time, and for the more plausible explanation other model systems are now under investigations.

(6) Kinetic data were treated as pseudo-first-order by the least-squares method ($r > 0.99$). The slope (k_{mead}) was corrected by substracting the blank rate to obtain the observed rate constant k_{obsd}. The second-order rate constant k_{cat} was then calculated by dividing k_{obsd} by the catalyst concentration. Thus obtained k_{cat} values are to be called apparent catalytic constants. $k_{cat} = k_{obsd}/[cat.]$.

(7) The pK_a values of imidazole of histidine are as follows: pK_1 = 6.04, pK_2 = 9.33.

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Synthetic Studies of the Nargenicins. Introduction of the C_{14}–C_{19} Side Chain by Diastereoselective [2,3] Wittig Rearrangement of a Tertiary Allylic Ether

Summary: The stereocontrolled [2,3] Wittig rearrangement of a tertiary allylic ether is employed to establish the remotely functionalized C_{14}–C_{19} macrolide fragment of an advanced intermediate related to the nargenicin macrolides.

Sir: The nargenicins[1] constitute a small family of macrolide antibiotics that have attracted synthetic attention as a result of their novel structure and activity against drug-resistant microorganisms.[2] Recently, we reported the first total synthesis of a naturally occurring nargenicin, 18-deoxynargenicin A_1 (**1b**).[3] A key step in our route to **1b** was the addition of an optically active fragment cor-

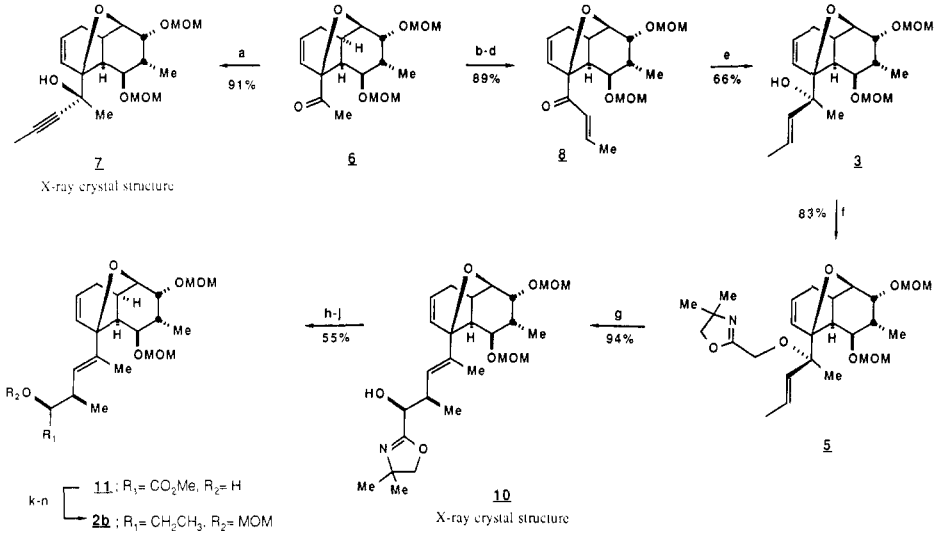
(1) Nargenicin A_1: Celmer, W. D.; Chmurny, G. N.; Moppett, C. E.; Ware, R. S.; Watts, P. C.; Whipple, E. B. *J. Am. Chem. Soc.* **1980**, *102*, 4203. Nodusmicin: Whaley, H. A.; Chidester, C. G.; Mizsak, S. A.; Wnuk, R. J. *Tetrahedron Lett.* **1980**, *21*, 3659. 18-Deoxynargenicin A_1: Whaley, H. A.; Coates, J. H., Abstract #187 from the 21st Interscience Conference of Antimicrobial Agents and Chemotherapy, November 4, 1981.

(2) Steliou, K.; Poupart, M.-A. *J. Am. Chem. Soc.* **1983**, *105*, 7130. (b) Kallmerten, J. *Tetrahedron Lett.* **1984**, *25*, 2843. (c) Jones, R. C. F.; Tunnicliffe, J. H. *Tetrahedron Lett.* **1985**, *26*, 5845. (d) Kallmerten, J.; Plata, D. J. *Heterocycles* **1987**, *25*, 145. (e) Roush, W. R.; Coe, J. W. *Tetrahedron Let.* **1987**, *28*, 931.

(3) Plata, D. J.; J. Kallmerten, J. *J. Am. Chem. Soc.* **1988**, *110*, 4041.

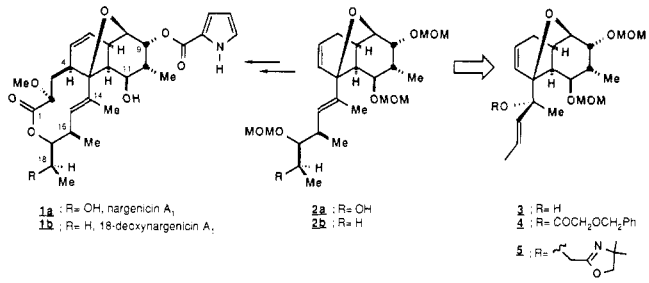
0022-3263/88/1953-5189$01.50/0

Scheme I[a]

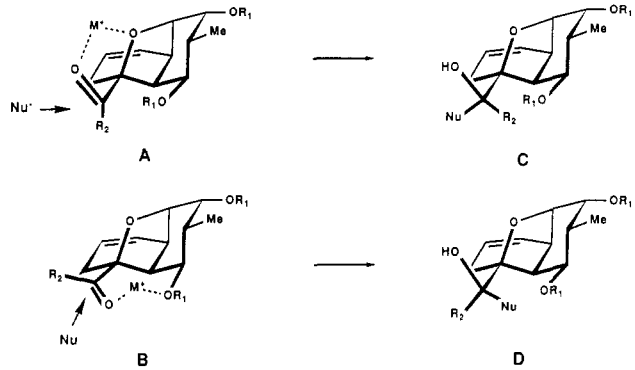


[a] Reagents: (a) $CH_3C{\equiv}CMgBr$, Et_2O, −78 °C; (b) LDA, THF, −78 °C, then MeCHO; (c) MsCl, NEt_3, THF, 0 °C; (d) DBU, THF, 25 °C; (e) MeLi, Et_2O, −78 °C; (f) KH, DME, $N{=}C(CH_2Cl)OCH_2C(CH_3)_2$ (**9**), reflux; (g) LDA, THF, −78 °C; (h) MeI (10 equiv, neat); (i) NaOH, H_2O–MeOH; (j) CH_2N_2, Et_2O, 0 °C; (k) $MeOCH_2Cl$, $(iPr)_2NEt$, CH_2Cl_2; (l) $LiAlH_4$, Et_2O, 0 °C; (m) TsCl, pyr; (n) Me_2CuLi, THF, −78 °C.

responding to the C_{14}–C_{19} subunit of the nargenicin macrolide system to a *racemic* precursor of the oxatricycloundecene nucleus, affording a 1:1 mixture of the advanced intermediate **2b** and its C_{16}–C_{17} diastereomer. While this strategy rapidly assembles the major structural elements of the nargenicin skeleton, it is relatively inefficient and not directly applicable to the synthesis of the 18-hydroxy nargenicin congeners, leading us to consider other schemes for introduction of the C_{14}–C_{19} fragment. We now report an alternative synthesis of **2b** in which the remote stereochemistry of the C_{14}–C_{19} side chain is developed in a stereorational, linear manner by the [2,3] Wittig rearrangement of tertiary allylic ether **5**.



Our approach is based on the well-documented 1,3 and 1,4 asymmetric transfer that accompanies [2,3] and [3,3] sigmatropic rearrangements of suitably functionalized allylic systems.[4] The desired relative stereochemistry at C_{16} and C_{17} of the nargenicin skeleton and the required C_{14}–C_{15} *E*-trisubstituted olefin could, in principle, result from either the enolate Claisen rearrangement[5] of tertiary allylic glycolate[6] **4** or the [2,3] Wittig rearrangement of tertiary allylic ether **5**.[7] Both routes are based on a common intermediate, allylic alcohol **3**, which we expected to be available from addition of an organometallic reagent to ketones **6** or **8**. At the outset of our studies, the diastereofacial preference for nucleophilic attack on these substrates was unclear. Addition of a nucleophile to conformation A, involving internal α-chelation[8] of the carbonyl group and the ether bridge, would afford an alcohol of configuration C; alternatively, addition to the seven-membered[9] chelate B (from coordination of the carbonyl with the C_{11} methoxymethyl substituent) would afford the diastereomeric D.



Initial efforts focused on development of a suitably functionalized allylic alcohol from ketone **6**, prepared by hydrolysis of the corresponding enol ether (Scheme I).[2d] Addition of propynyl Grignard reagent to **6** was completely selective, yielding alcohol **7**,[10] as determined by X-ray crystallography.[11a] The formation of **7** is consistent with

(4) (a) Ziegler, F. E. *Acc. Chem. Res.* **1977**, *10*, 227. (b) Hill, R. K. In *Asymmetric Synthesis* Morrison, J. D., Ed.; Academic Press: New York, 1984; Vol. 3, pp 503–572. (c) Bartlett, P. A. *Tetrahedron* **1980**, *36*, 2. (d) Nakai, T.; Mikami, K. *Chem. Rev.* **1986**, *86*, 885.

(5) (a) Ireland, R. E.; Muchmore, D. C.; Hengartner, U. *J. Am. Chem. Soc.* **1972**, *94*, 5098. (b) Ireland, R. E.; Pfister, G. *Tetrahedron Lett.* **1969**, 2145.

(6) (a) Gould, T. J.; Balestra, M.; Wittman, M. D.; Gary, J. A.; Rossano, L. T.; Kallmerten, J. *J. Org. Chem.* **1987**, *52*, 3889. (b) Burke, S. D.; Fobare, W. F.; Pacofsky, G. J. *J. Org. Chem.* **1983**, *48*, 5221. (c) Kallmerten, J.; Gould, T. J. *Tetrahedron Lett.* **1983**, *24*, 5177.

(7) Wittman, M. D.; Kallmerten, J. *J. Org. Chem.* **1988**, *53*, in press.

(8) Still, W. C.; McDonald, J. H. *Tetrahedron Lett.* **1980**, *21*, 1031.

(9) Recent examples where seven-membered chelation complexes can be invoked to rationalize the stereochemistry of nucleophilic addition to a carbonyl group include the following: (a) Barrish, J. C.; Lee, H. L.; Baggliolini, E. G.; Uskokovic, M. R. *J. Org. Chem.* **1987**, *52*, 1372. (b) Smith, A. B.; Schow, S. R.; Bloom, J. D.; Thompson, A. S.; Winzenberg, K. N. *J. Am. Chem. Soc.* **1982**, *104*, 4015.

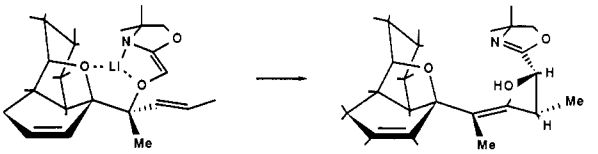
(10) The spectroscopic properties of all new compounds reported herein are in agreement with the structures assigned. With the exception of the unstable ether **5**, all new compounds gave satisfactory combustion analyses.

(11) (a) Pfluger, C.; Ostrander, R.; Plata, D. J.; Kallmerten, J., submitted for publication. (b) Pfluger, C.; Ostrander, R.; Kallmerten, J.; Rossano, L. T., manuscript in preparation.

net *si* addition to **6**, suggesting that nucleophilic attack occurs via the α-chelate A. With these results in hand, enone **8** was prepared by addition of the lithium enolate of **6** to acetaldehyde, followed by mesylation of the aldol product and base-induced elimination. Addition of methyllithium to **8** provided alcohol **3** in addition to small amounts of the 1,4 adduct. Comparison of **3** to the allylic alcohol derived from $LiAlH_4$ reduction of **7** clearly indicated these intermediates to be epimeric at the exocyclic center.

We next attempted to prepare a suitable derivative of **3** for use as an enolate Claisen substrate. Unfortunately, all attempts to acylate the tertiary alcohol met with failure, presumably as a result of the extremely hindered nature of this center.[12] Interestingly, alkylation of **3** was quite straightforward, and we turned our attention to the [2,3] Wittig rearrangement[7,13] as an alternative procedure for sigmatropic homologation. Treatment of **3** with (chloromethyl)oxazoline **9**[14] (KH, DME, 25 °C) gave ether **5**, which, when exposed to base, underwent a highly diastereoselective rearrangement to give oxazoline **10**. That we had indeed established the desired olefin geometry and correct remote stereochemistry at C_{16} and C_{17} was confirmed by X-ray crystallographic analysis.[11b] The diastereoselectivity of this [2,3] Wittig rearrangement is consistent with that observed for related acyclic substrates,[7] wherein coordination of the α-alkoxy substituent (in the case of **5**, the ether bridge) with the enamide counterion serves as the control element that ultimately directs the stereochemical outcome of the sigmatropic event.

Conversion of **10** to the known **2b** was accomplished in seven steps beginning with hydrolysis of the oxazoline and esterification with diazomethane to give **11**. Ester **11** was



E 10

transformed to (±)-**2b** by a sequence consisting of (1) protection of the free hydroxyl group, (2) reduction with $LiAlH_4$, (3) tosylation of the primary alcohol, and (4) displacement with lithium dimethylcuprate, yielding (±)-**2b**, identical in all respects (except optical rotation) with an authentic sample.[3]

In summary, we have completed a synthesis of the key nargenicin intermediate **2b**, in which the remote chirality of the nargenicin macrolide system is introduced in a stereorational manner by the [2,3] Wittig rearrangement of a tertiary allylic ether. This linear scheme offers an advantage in efficiency over our previously reported convergent route and demonstrates the potential of the tertiary [2,3] Wittig rearrangement for the development of remote stereochemical relationships across a geometrically defined trisubstituted olefin. We note that oxazoline **10** represents an entry to C_{18}-functionalized intermediates (i.e., **2a**) from which the synthesis of the C_{18}-oxygenated nargenicin congeners can be addressed.

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Supplementary Material Available: Experimental procedures and analytical data for all new compounds and tables listing crystallographic details for **7** and **10**, including final atomic coordinates, bond lengths and angles, and anisotropic thermal parameters for non-hydrogen atoms (20 pages). Ordering information is given on any current masthead page.

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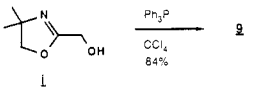
(12) Degradation studies on the parent macrolides provide an indication of the extreme steric compression experienced by external reagents in this region. For example, the C_{14}–C_{15} olefin of 18-deoxynargenicin A_1 is unreactive to oxidation with ozone, peracids, or osmium tetraoxide and hydrogenation under heterogeneous or homogeneous conditions: Plata, D. J. Ph.D. Dissertation, Syracuse University, 1987.

(13) Mikami, K.; Fujimoto, K.; Nakai, T. *Tetrahedron Lett.* **1983**, *24*, 513.

(14) Oxazoline **9** is prepared by chlorination of the known α-hydroxy oxazoline *i* (Pridgen, L. N.; Miller, G. *J. Heterocycl. Chem.* **1983**, *20*, 1223):



i

M. Wittman, Syracuse University, unpublished results.