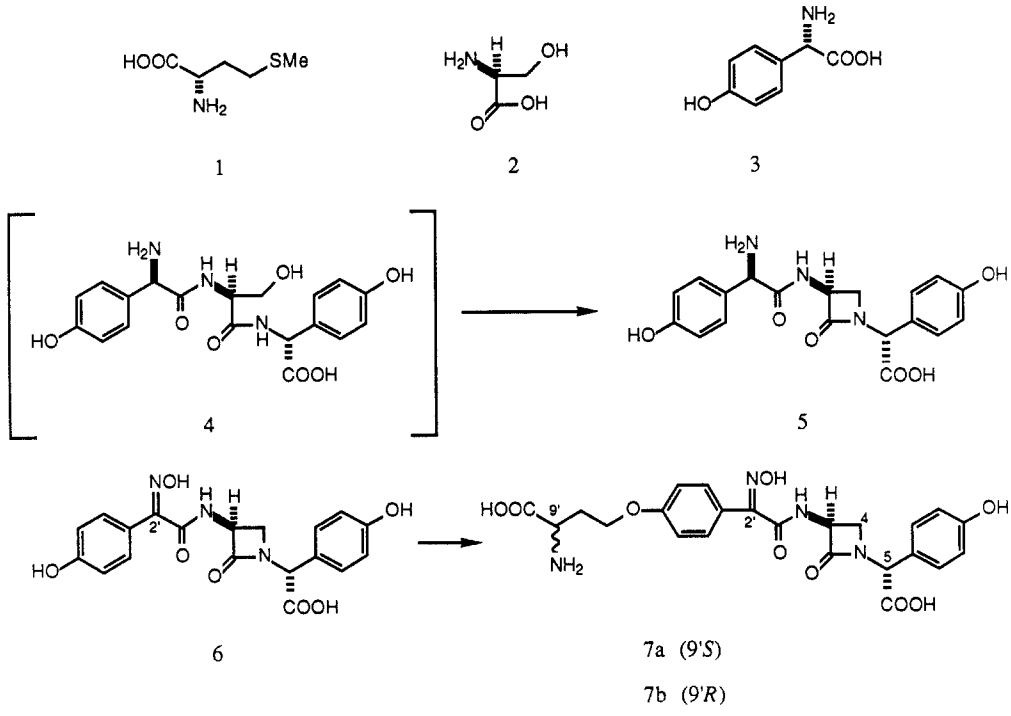
Scheme I



mixture of [2′-^{13}C]nocardicin G and epinocardicin G[3] by selective transformation of the 2′-amino function to the *syn*-oxime of **6**[15] and purified by preparative HPLC. In five large-scale cell-free incubations, [2′-^{13}C]nocardicin E (19.7 mg) was completely converted to a mixture of [2′-^{13}C]isonocardicin A and nocardicin A in the presence of an approximately 2.5 molar excess of AdoMet. Proteins were precipitated by brief heat denaturation, and the mixture of labeled **7a**/**7b** was isolated by ion exchange (DEAE Sephadex A-25) and absorption (Amberlite XAD-4) chromatography followed by crystallization from water (pH 2.5).[1] The intact incorporation of [2′-^{13}C]-**6** into the **7a**/**7b** (20 mg) isolated was demonstrated by the presence of a single enhanced resonance[23] at 153.98 ppm in its ^{13}C{^{1}H} NMR spectrum corresponding to the C-2′ oxime carbon of the product.[2] Addition of a small amount of [2′-^{13}C]-**6** resulted in the appearance of a second signal at 154.37 ppm. Further ^{1}H NMR and HPLC analysis confirmed the identity of the product as **7a**/**7b** (vide supra).

In conclusion, we have obtained a partially purified cell-free system from *N. uniformis* exhibiting two enzymic activities involved in the late stages of nocardicin A biosynthesis. The first, a 3-amino-3-carboxypropyl transferase, carries nocardicin E (**6**) and AdoMet (but not L-methionine and ATP) to isonocardicin A (**7a**), and the second, an epimerase, inverts the C-9′ configuration of **7a** to give nocardicin A (**7b**). Under normal conditions of fermentation the latter is selectively transported out of growing cells to give nocardicin A as the principal metabolite of the pathway. The group-transfer reaction from AdoMet has been shown to proceed with inversion of configuration,[11] paralleling the stereochemical course of polyamine biosynthesis[12] from decarboxylated AdoMet. On the basis of these findings an overall biosynthetic route to nocardicin A, and quite probably the major one, may now be more clearly defined (see Scheme I). Nocardicin G (**5**) is the first β-lactam-containing intermediate of the pathway[3] and originates from the amino acids **2** and **3**, presumably by way of the hypothetical tripeptide **4** or a closely related derivative. Nocardicin G (**5**) is then elaborated to the remaining six members of this antibiotic family,[24] but, specifically, amine oxidation must yield the 2′-*syn*-oxime of nocardicin E (**6**) which serves as the nucleophilic partner to AdoMet, in an S_N2 transfer[11] of a 3-amino-3-carboxypropyl group, to give isonocardicin A (**7a**). An epimerase then acts to convert the latter to nocardicin A (**7b**). Purification of the 3-amino-3-carboxypropyl transferase is in progress, and its detailed role in the biosynthesis of the nocardicins will be reported in due course.

Acknowledgment. We are deeply grateful to L. T. Nguyen for many preliminary cell-free experiments that eventually made possible the successful transformations reported here and to the NIH (AI 14937) for sustained financial support. Major analytical instrumentation used in this research was acquired with funds from the NIH and the NSF (NMR: RR 01934 and PCM 83-03176; MS: RR 02318).

(23) Even though a mixture of **7a** and **7b** was obtained, a single resonance was observed for C-2′.

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Metal-Catalyzed Cyclization via Isomerization of α-Dienyl-ω-allyl Acetates

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It can be argued that the most effective approach for construction of organic molecules involves a process where the combined elemental compositions of the substrates are equivalent to that of the final product. In cyclizations, such a process corresponds to an isomerization of an acyclic system to a desired ring. Besides processes such as intramolecular cycloadditions,[1,2] reactions of this type, exemplified by the intramolecular Alder ene reaction[1b,3,4] and transition-metal-catalyzed cyclizations of enynes,[5]

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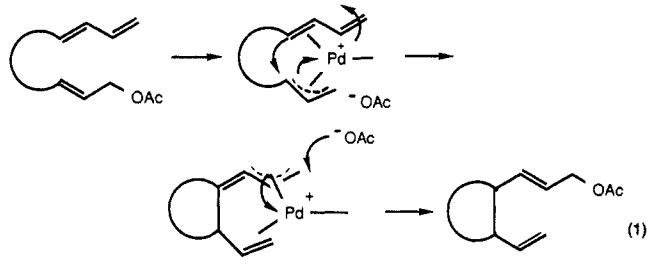
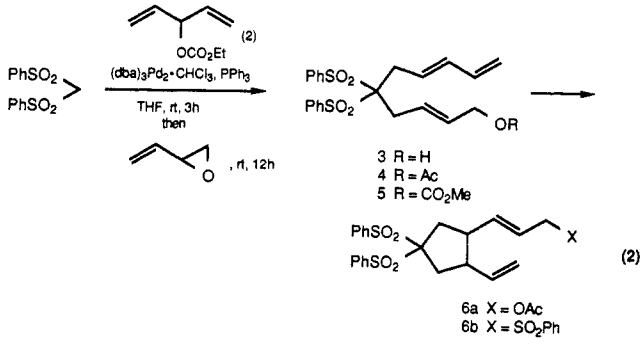
enals,[6] and of substrates bearing vinyl epoxides and pronucleophiles at the two termini,[7] normally involve migration of protons. The importance of oxygen, both from the point of view of its presence in many of the final products desired and of its utility for further structural elaboration, suggested that processes involving migration of such groups could be particularly useful.[8] We wish to report a facile palladium-catalyzed cyclization that simply isomerizes α-dienyl-ω-allyl acetates.

The concept is illustrated in eq 1 in which the conversion of a carbon–carbon π-bond to a σ-bond provides a driving force.[9]



(1)

The ease of availability of the cyclization substrates makes such a process particularly attractive. For example, sequential Pd(0) catalyzed allylic alkylations of bis(benzenesulfonyl)methane with ethyl 1,4-pentadien-3-yl carbonate (**2**)[10] and then 3,4-epoxy-1-butene[11] in a single pot gives the alcohol **3** directly in 64% isolated yield. Acetylation under standard conditions provides the substrate **4**.[12]

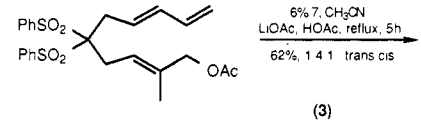


(2)

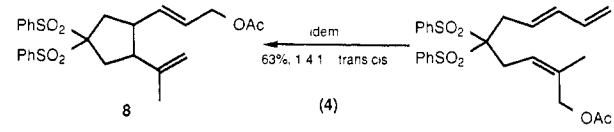
Initial results proved disappointing. Subjecting **4** to $(dba)_3Pd_2{\cdot}CHCl_3$ (**7**) in refluxing THF, chloroform-*d*, or benzene-d_6 or at 90 °C in DMSO-d_6 gives no reaction. Nevertheless, acetonitrile-d_3 dramatically changes the reactivity profile and provides the cyclization product **6a**[12] in 60–70% yield as a single *E*-olefin isomer but a 2.3:1 mixture of trans:cis ring stereoisomers. Slight improvements in yield occur by adding 1 equiv of acetic acid or 1 equiv of lithium acetate or better by adding 1 equiv of each (to 80–87%). Addition of triphenylphosphine or triisopropyl phosphite (even 1 equiv per Pd)[13] effects cyclization in diminished yield (35–40%) with enhanced trans selectivity (trans:cis 9:1) but as a tris-sulfone **6b**.[12] Replacing acetonitrile by acetic acid also leads to the normal cyclized product **6a** at 90 °C in slightly lower yields (71%, 2.5:1 trans:cis). Our standard conditions for cyclization involves 6% of Pd(0) complex **7** in acetonitrile containing 1 equiv each of acetic acid and lithium acetate in the absence of any phosphorus ligands.

The excellent reactivity of allyl carbonates toward Pd(0) catalysts[10] led us to investigate their behavior. Whereas subjecting carbonate **5** to Pd(0) catalyst **7** in acetonitrile led only to an elimination product, the addition of 1 equiv each of lithium acetate and acetic acid to the acetonitrile leads to smooth cyclization (80% yield) to produce allylic acetate **6**.[12]

Equations 3 and 4 compare the effect of the olefin geometry of the allyl acetate on the cyclization process. Neither the yield (62–63%) nor the stereochemistry (trans:cis 1.4:1) show any dependence on the double bond geometry of the starting material.

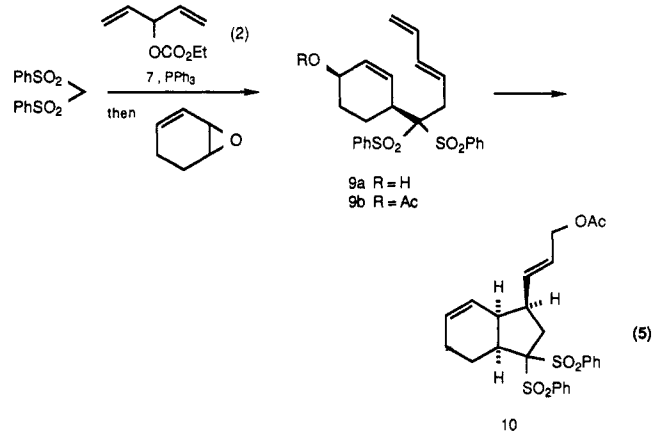


(3)



(4)

Equation 5 illustrates the utility of this approach as an annulation method. The alcohol **9a** is available in a single pot sequential Pd(0) catalyzed allylic alkylation (49%). Cyclization of the



(5)

10

corresponding acetate **9b** in acetic acid with **7** at 105 °C gives a 56% yield of **10**[12] as a crystalline single isomer, mp 146–7 °C. The stereochemistry of the product, possessing the thermodynamically less stable cis-fused stereoisomer with the side chain in an endo orientation, is assigned based upon the NMR spectral data as summarized in the Supplementary Material.

The high diastereoselectivity in forming the bicyclic product **10** led us to reconsider the question of diastereoselectivity in the formation of the monocyclic products. Indeed, the monosulfone **11**, easily available by selective reductive monodesulfonylation of **3**[14] (6% Na(Hg), 3:1 THF/methanol, HOAc, −10 °C) and standard acetylation (75% for the two steps), cyclizes using 6% of catalyst **7** and stoichiometric amounts of sodium acetate and acetic acid in acetonitrile to give a diastereomerically pure product **12**[12] in 68% yield. The cis assignment of the two carbon chains

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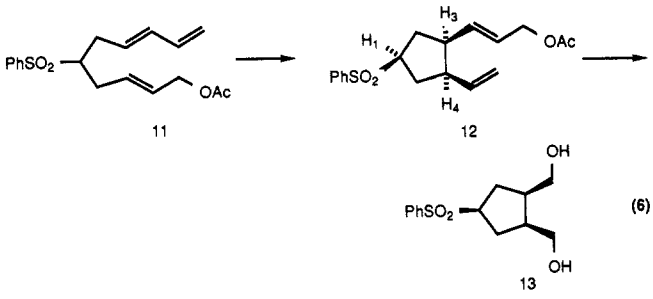
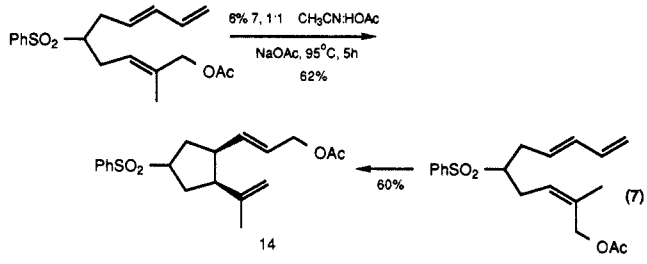
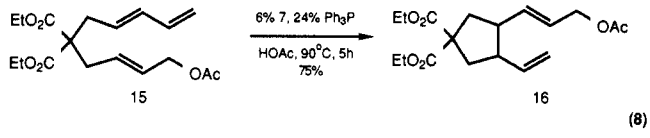


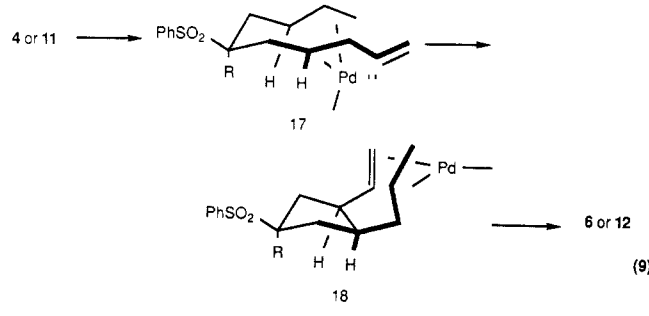
derives from conversion to diol **13**[12] [O_3, CH_2Cl_2, CH_3OH, −78 °C then $NaBH_4$, CH_3OH, 83%]. ^{13}C NMR spectroscopy reveals that **13** has a plane of symmetry [δ 62.69, t, 2 C; 62.57, d, 1 C; 42.91, d, 2 C; 29.08, t, 2 C] which requires the hydroxymethyl groups to be cis. A 7% NOE between H(1) and H(3) + H(4) suggests a cis relationship of these protons and, therefore, the cis stereochemistry of the phenylsulfonyl group. The high diastereoselectivity of this cyclization is independent of the olefin geometry of the starting material (eq 7).



In contrast to the sulfone-substituted substrates, the malonate-derived substrate **15** requires the use of triphenylphosphine for effective cyclization. The source of this difference remains an area of active investigation.



This new synthesis of cyclopentane rings based upon the principle of cyclization via isomerization can provide a stereocontrolled approach to the thermodynamically less stable cis isomers. The high stereoselectivity is in accord with a reorganization in the ligand sphere from one π-allylpalladium–olefin complex such as **17** to another such as **18** with formation of a carbon–carbon bond as shown in eq 9. The interaction of a bulky



R group in **17** with the palladium template would destabilize transition states involving a pathway proceeding through **17** to give **18**. The fact that the trans isomer dominates when R = $PhSO_2$ in **17** and the cis isomer is the exclusive product when R = H suggests that we may have access to either diastereomer depending upon the substitution pattern on the tether.

The fact that the product retains an allyl acetate moiety which is reactive toward the types of catalysts employed makes the success of this cyclization via isomerization rather remarkable. Obviously, the functionality generated in the product offers an opportunity for further structural elaboration.

Acknowledgment. We thank the National Science Foundation and the National Institutes of Health, General Medical Sciences Institute, for their generous support of our programs. Mass spectral data was graciously provided through the Mass Spectrometry Facility, University of California—San Francisco, supported by the NIH Division of Research Resources.

Registry No. 2, 116997-87-6; **3**, 116997-88-7; **4**, 116997-89-8; **5**, 116997-90-1; *cis*-**6a**, 116997-99-0; *trans*-**6a**, 117065-70-0; *cis*-**6b**, 116998-00-6; *trans*-**6b**, 117065-71-1; *cis*-**8**, 116998-01-7; *trans*-**8**, 117065-72-2; **9a**, 116997-93-4; **9b**, 116997-94-5; **10**, 117024-47-2; **11**, 116997-96-7; **12**, 116998-04-0; **13**, 116998-05-1; **14**, 116998-02-8; **15**, 116997-98-9; **16**, 116998-03-9; $PhSO_2CH_2SO_2Ph$, 3406-02-8; (*E*,*E*)-H_2C=CHCH=CHCH$_2$C(SO_2Ph)$_2$$CH_2$CH=C($CH_3$)$CH_2OAc$, 116997-91-2; (*Z*,*E*)-H_2C=CHCH=CHCH$_2$C(SO_2Ph)$_2$$CH_2$CH=C($CH_3$)$CH_2OAc$, 116997-92-3; (*E*,*E*)-H_2C=CHCH=CHCH$_2$CH(SO_2Ph)CH_2CH=C(CH_3)CH_2OAc, 116997-95-6; (*Z*,*E*)-H_2C=CHCH=CHCH$_2$CH(SO_2Ph)CH_2CH=C(CH_3)CH_2OAc, 116997-97-8; 3,4-epoxy-1-butene, 930-22-3; 3,4-epoxy-1-cyclohexene, 6705-51-7.

Supplementary Material Available: Spectral data for **6a**, **6b**, **8**, **10**, **12**, **14**, and *trans*-**16** (4 pages). Ordering information is given on any current masthead page.

Does the Conformation of Hydrocarbon Chains Depend on Solvation?

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Modern theoretical and instrumental methods have failed to resolve many simple yet significant chemical questions. This communication addresses one of them: How are the conformations of hydrocarbon chains affected by solvation? The question is significant because hydrocarbon chains embedded in solvent are among the most important structural units in chemistry and biology. Within a crystal, aliphatic hydrocarbons assume extended, all-trans geometries.[1] On the other hand, *n*-butane in the gas phase contains about 25% gauche rotamer.[2] Only 16% of gaseous *n*-heptane is all-trans.[3] Matters are, however, far less definitive with the liquid state. The origins of the trans/gauche energy difference are not completely understood,[4] and even less is known about how solvation influences the controlling elements. Access to chain behavior in solution has been hampered by computational complexities and a poor experimental approachability.

Conformational data on hydrocarbon chains in solution are, of course, available although often in conflict. Thus, Jorgensen et al.[5] have repeatedly found in Monte Carlo simulations that hydrocarbons (e.g., butane, pentane, and hexane) do not experience conformational changes upon transfer from the gas phase to neat liquids. In contrast, spectroscopic studies[6-8] indicate a marked phase-sensitivity for *n*-butane. According to computations of Pratt et al.,[9] the more globular gauche form is favored in the condensed phase where molecules are close enough for repulsive interactions

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