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Studies toward the Synthesis of Oximidines I and II

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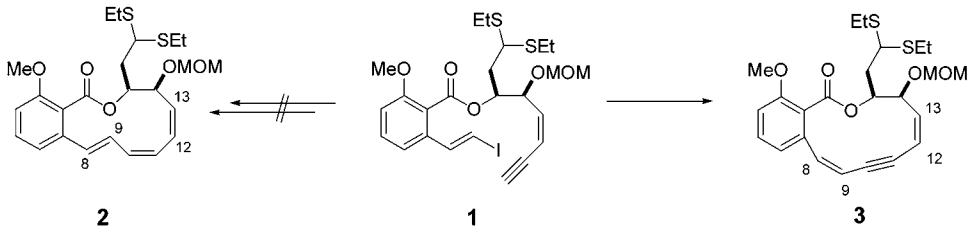
ABSTRACT



The synthesis of compound 1, a precursor for the synthesis of the oximidine II core structure 2, is described. An undesired C8–C9 isomerization occurred during the intramolecular Castro–Stephens reaction leading to macrocyle 3. The thermodynamic driving force for this unexpected isomerization was established by DFT and MP2 calculations.

The oximidines I and II[1] (**4** and **5**, Figure 1) belong to a family of recently discovered macrolides, which contain a salicylic acid moiety and an unusual enamide side chain. This family of natural products also includes the salicylihalamides, the apicularens, and the lobatamides.[2] The common biological targets of these natural products have been identified as mammalian vacuolar-type (H^+)-ATPases.[3] The possibility of forming structural analogues to gain more information about the mechanism of action has inspired researchers to develop total syntheses toward these compounds. The first total synthesis of the oximidines I and II, isolated from *Pseudomonas sp.* in 1999,[1] was reported in 2003.[4] Further synthetic efforts have been limited to model studies for the formation and the installation of the enamide side chain[5] and to the preparation of simplified macrocyclic core structures.[6−8] We are now reporting on our approach toward a synthesis of the fully functionalized oximidines I and II.

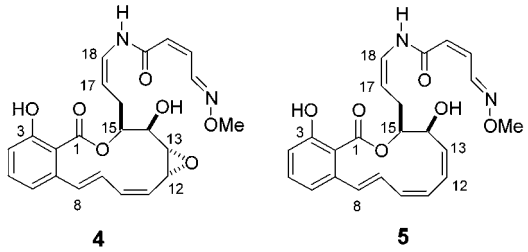


Figure 1. Oximidines I (**4**) and II (**5**).

Assuming that it might be possible to transform the C12−C13 double bond in oximidine II (**5**) into the corresponding

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(1) Kim, J. W.; Shin-ya, K.; Furihata, K.; Hayakawa, Y.; Seto, H. *J. Org. Chem.* **1999**, *64*, 153−155.
(2) For a review see: Yet, L. *Chem. Rev.* **2003**, *103*, 4283−4306.
(3) Boyd, M. R.; Farina, C.; Belfiore, P.; Gagliardi, S.; Kim, J. W.; Hayakawa, Y.; Beutler, J. A.; McKee, T. C.; Bowman, B. J.; Bowman, E. J. *J. Pharmacol. Exp. Ther.* **2001**, *297*, 114−120.
(4) Wang, R.; Porco, J. A., Jr. *J. Am. Chem. Soc.* **2003**, *125*, 6040−6041.
(5) (a) Shen, R.; Porco, J. A., Jr. *Org. Lett.* **2000**, *2*, 1333−1336. (b) Raw, S. A.; Taylor, R. J. K. *Tetrahedron Lett.* **2000**, *41*, 10357−10361. (c) Snider, B. B.; Song, F. *Org. Lett.* **2000**, *2*, 407−408. (d) Kuramochi, K.; Watanabe, H.; Kitahara, T. *Synlett* **2000**, 397−399.

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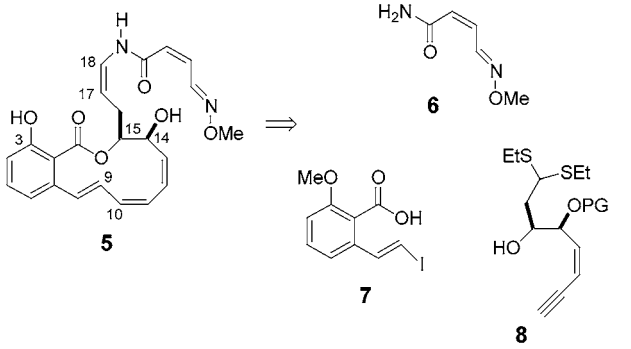
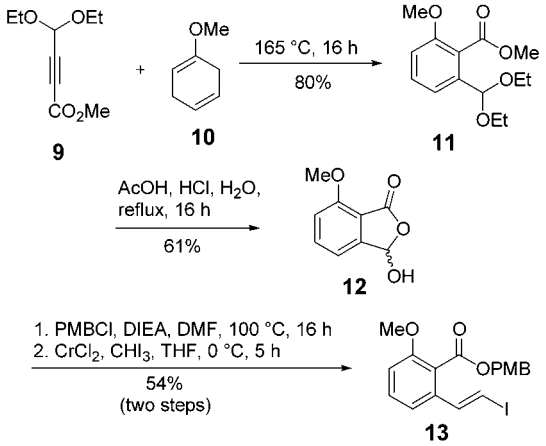
epoxide leading to oximidine I (**4**), we focused our efforts on a total synthesis of oximidine II (**5**). The main challenge in a total synthesis of **5** is the formation of the strained 12-membered macrocycle containing nine sp^2 carbon centers. Our retrosynthetic disconnections are set at the ester bond, at the enamide between carbons C17 and C18, and between carbons C9 and C10 leading to fragments **6**, **7**, and **8** (Scheme 1).

Scheme 1



Since the enamide side chain is presumably chemically unstable, we aimed first at the preparation of the macrocycle from fragments **7** and **8**. The subsequent installation of the side chain with amide **6** requires an appropriate elongation of the protected aldehyde in **8**. For the preparation of the 1,2,3-trisubstituted aromatic fragment **13** we selected the synthetic route shown in Scheme 2. The Diels−Alder reaction[9,10] between alkyne **9** and diene **10** forms the desired salicylate **11** in 80% yield.

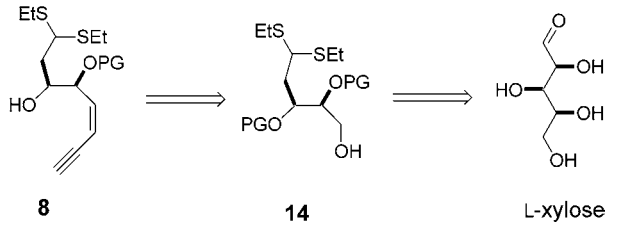
Scheme 2



Acidic hydrolysis[9] of **11** yielded isobenzofuranone **12**, which was transformed to the trans iodide **13** by a two-step process by using an esterification and a Takai-olefination. A 1:4 cis:trans mixture of **13** was obtained, which was separable by silica gel chromatography.

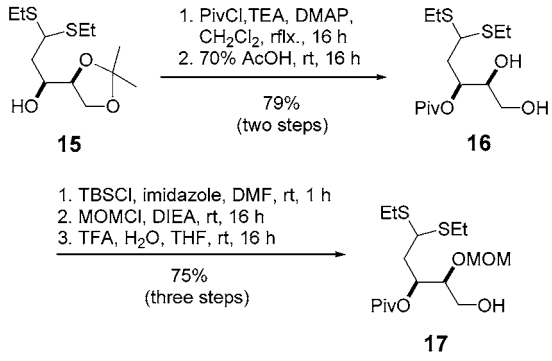
We chose a chiral-pool strategy for the preparation of the aliphatic building block. Compound **8** can be obtained from protected 2-deoxysugar **14**, which is a derivative of L-xylose (Scheme 3).

Scheme 3



Utilizing a modified literature procedure[11,12] L-xylose was transformed into known alcohol **15** in 70% yield over four steps. The alcohol functionality was protected as pivaloate ester and removal of the acetonide in 70% acetic acid at room temperature provided diol **16**. A three-step sequence involving TBS-protection of the primary alcohol in **16**, MOM protection of the secondary alcohol followed by removal of the silyl group, provided the primary alcohol **17** in 75%

Scheme 4



overall yield. Dess−Martin oxidation of the primary alcohol (Scheme 5) furnished the unstable corresponding aldehyde, which was immediately subjected to a Corey−Fuchs reaction. The resulting dibromoalkene was stereoselectively debrominated to form *cis*-vinyl bromide **18** in 71% overall yield. Removal of the pivaloate with DIBAL-H, Sonogashira

(6) Scheufler, F.; Maier, M. E. *Synlett* **2001**, 1221−1224.
(7) Coleman, R. S.; Garg, R. *Org. Lett.* **2001**, *3*, 3487−3490.
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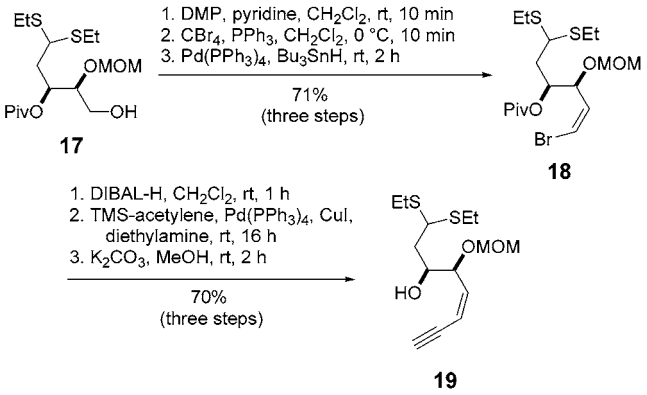
(12) Wong, M. Y. H.; Gray, G. R. *J. Am. Chem. Soc.* **1978**, *100*, 3548−3553.

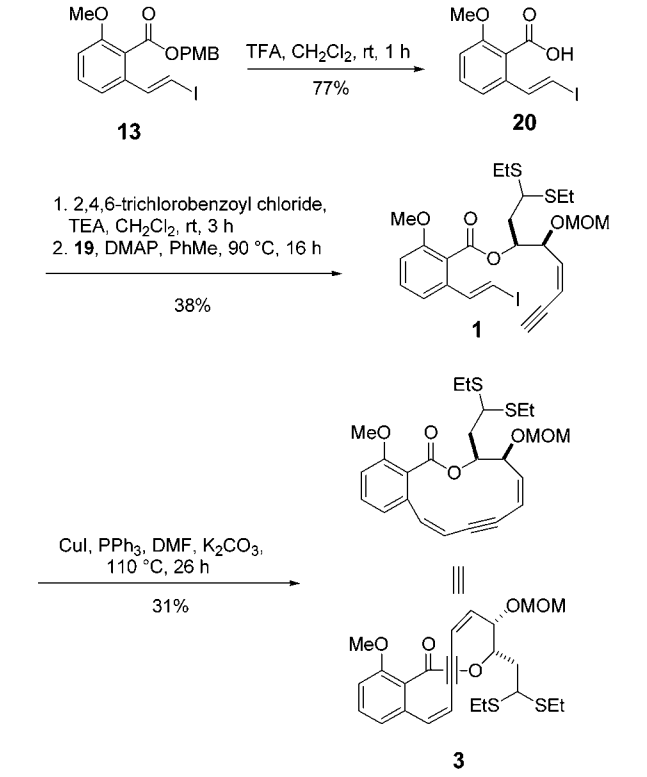
Scheme 5



elongation, and subsequent deprotection of the alkyne under mild nucleophilic conditions gave the desired aliphatic building block **19**.

With the two building blocks **13** and **19** in hand, our next aim was the formation of the macrocyclic core structure of oximidine II. Our strategy was the saponification of **13**, esterification of resulting **20** with **19**, and a macrocyclization under Castro−Stephens conditions.[7] Ester hydrolysis of **13** was achieved with TFA/CH_2Cl_2 to give acid **20** in 77% yield (Scheme 6). The subsequent esterification with **19** was difficult because of the low reactivity of the acid moiety due to steric and electronic reasons. However, following the Yamaguchi procedure we were able to form the desired ester

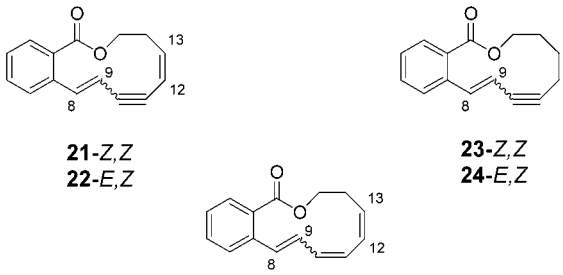
Scheme 6



1 in low yield. Compound **1** is a fully functionalized precursor for an intramolecular Castro−Stephens reaction.[7] Reaction of **1** under Castro−Stephens conditions yielded macrocycle **3** that arises from the desired intramolecular sp−sp^2 coupling. Generally, this reaction is stereospecific with respect to the precursor vinyliodide,[13] and in the present case a trans C8−C9 double bond was expected. However, NMR analysis yielded a coupling constant of $^3J = 12$ Hz for the double bond, a difference of 4 Hz by comparison with the results from Coleman and Garg,[7] who reported a value of $^3J = 16$ Hz for trans-configured C8−C9 centers in several model systems.

To put these values in perspective, we calculated Z and *E* vicinal ^3J(H,H) values across C8−C9 for the global minimum energy conformations (see below) of model systems **21** and **22** (Scheme 7). The coupling constants were obtained by computing the four contributing terms according to Ramsey's non-relativistic approach[14] in the context of the B3LYP/6-311G(d,p) method.[15]

Scheme 7



Summing the Ramsey contributions furnishes ^3J(H,H) values of 14.2 and 20.4 Hz, respectively (Table 1). Since the predicted ^3J(H,H) values are slightly overestimated by comparison to the experimental values, we scaled the predictions by employing the *Z* and *E* ^3J values of acrylonitrile as standards ($\Delta^3J = -2.4$ and -4.5 Hz, respectively; Table 1). In this way, the values for **21** and **22** are reduced to 11.8 and 15.9 Hz, respectively, in complete accord with the experimental values of 12 and 16 Hz. To test whether the aromatic methoxy substituent in **3** might lower the *E*-^3J from 16 to 12 Hz, truncated forms of **22** and **3** (**27** and **28**, respectively; see Supporting Information) were subjected to coupling constant analysis (Table 1). The methoxy perturbation has no influence on the vicinal ^3J value.

We conclude that compound **3** is the *Z*,*Z* isomer. A strong NOE between the protons at C8 and C9 supports this deduction. Presumably, isomerization took place from the

(13) (a) Kabbara, J.; Hoffmann, C.; Schinzer, D. *Synthesis* **1995**, 299−302. (b) von der Ohe, F.; Bruckner, R. *New J. Chem.* **2000**, *24*, 659−669. (c) Rawat, D. S.; Zaleski, J. M. *Synth. Commun.* **2002**, *32*, 1489−1494.

(14) Ramsey, N. F. *Phys. Rev.* **1953**, *91*, 303−307.

(15) For definitions of the various terms and the method of calculation, see: Barone V.; Peralta, J. E.; Contreras, R. H.; Snyder, J. P. *J. Phys. Chem. A* **2002**, *106*, 5607−5612.

Table 1. Ramsey Contributions and $^3J(H,H)^{total}$ (Hz) for C8−C9 with the DFT B3LYP/6-311G(d,p) Model

	DSO	PSO	FC	SD	total
21	−0.002	−0.57	14.78	−0.052	14.2
22	−2.74	3.02	19.72	0.39	20.4
***Z*-A**[a,b]	−0.76	0.072	14.89	−0.043	14.2[c]
***E*-A**[a,b]	−3.30	4.77	20.56	0.33	22.4[c]
27	−2.84	3.05	19.64	0.40	20.2
28	−2.81	4.39	19.67	0.40	21.7

[a] ^3J(H,H) for acrylonitrile ***Z*-A** and ***E*-A** are 11.8 and 17.9 Hz, respectively: (i) http://chemistry.utah.edu/faculty/vogler/LectureNotes331/CH331Chapter13.pdf; (ii) Lambert, J. B.; Shurvell, H. F.; Lightner, D. A.; Cooks, R. G. In *Organic Structural Spectroscopy*; Prentice Hall: Englewood Cliffs, NJ, 1998; p 72. [b] Geometry optimized with the B3LYP/6-311G(d,p) model. [c] ^3J scaling factors from *Z* and *E* acrylonitrile are −2.4 and −4.5 Hz, respectively.

E to a *Z* double bond under the reaction conditions. The reasonableness of these assertions was evaluated by performing exhaustive conformational analyses on model structures **21**-*Z*,*Z* and **22**-*E*,*Z* as well as on the corresponding dihydro analogues **23**−**26**. Table 2 summarizes the results and includes both molecular mechanics and quantum chemical relative energies for the C8−C9 configurational isomers. For **21** and **22** with three unsaturated centers, the *Z*,*Z* form is predicted to be more stable by 11−16 kcal/mol, highlighting the thermodynamic basis for isomerization.

Table 2. Relative Energies of Annelated and Unsaturated 12-Membered-Ring Lactones (kcal/mol)[a]

	Δ*E*(rel), kcal/mol		
	MMFF[b]	DFT[c]	MP2[d]
21	0.0	0.0	0.0
22	11.4	14.4	15.7
23	0.0	0.0	0.0
24	10.9	7.5	9.0
25	4.8	2.6	2.4
26	0.0	0.0	0.0

[a] Only MMFF global minima derived by Monte Carlo conformer searching are compared. [b] Molecular mechanics/MMFF energies. [c] B3LYP/6-311G(d,p)//MMFF. [d] MP2/6-311G(d,p)//MMFF (see Supporting Information).

Reduction of the C12−C13 double bond (i.e. **23** and **24**) is predicted to lower the energy difference, but to still favor the *Z*-form **23** by 7−11 kcal/mol. On the other hand, the calculations suggest that reduction of the acetylene to a cis double bond (i.e. **25** and **26**)[7] reverses the stability order to favor **26**-*E*,*Z*,*Z* by 2−5 kcal/mol. These results imply that the presence of the acetylene unit at C10−C11 is decisive for determining the relative stability of the C8−C9 double bond isomers; namely, the presence of the acetylene unit in the 12-membered ring stabilizes the C8−C9 *Z*-alkene. That this carries over to **3** was shown by substituent supplementation of the MMFF global minima of **21** and **22** followed by MMFF optimization to give **3** in a twisted conformation and the corresponding trans isomer. The former is favored by 15.3 kcal/mol (ΔE_{rel}, MMFF).

In summary, we have developed a convenient synthesis of an aromatic and an aliphatic building block of the fully functionalized macrocycle of oximidine II. We have also combined these building blocks to the desired core structure, albeit with the *Z*-configured C8−C9 double bond. In addition, DFT and MP2 calculations were used to determine the thermodynamic driving force for this isomerization. Further investigations toward the use of the building blocks for the synthesis of the oximidines are currently in progress.

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Supporting Information Available: Experimental procedures including physical data for all synthesized compounds; Ramsey term contributions to ^3J(H,H) and computational details. This material is available free of charge via the Internet at http://pubs.acs.org.

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