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Stereocontrolled Synthesis of Cyclopropanol Amino Acids from Allylic Sulfones: Conformationally Restricted Building Blocks

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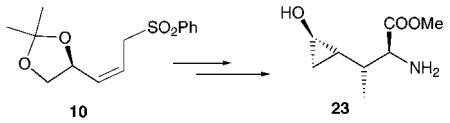
ABSTRACT



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A new amino acid methyl ester with a cyclopropanol has been synthesized starting from the allyl sulfone 10. The starting material, 10, could be obtained in both enantiomeric forms. The stereoselectivity of the cyclopropane formation has been studied by molecular modeling.

The cyclopropane ring is present in a wide variety of naturally occurring compounds, many of these with interesting biological activities.[1] Although there are not many naturally occurring amino acids containing a cyclopropyl group,[2] a recently isolated natural product, belactosin A, **1** (Figure 1), contains a (2*S*,1′*R*,2′*S*)-3-(*trans*-2-aminocyclopropyl)alanine amino acid **2** as its core feature. This interesting natural product modulates cell-cycle progression via inhibition of cyclin-cdk complexes, showing weak antitumor activity.[3]

Up to the present time, only two syntheses of this amino acid **2** have been reported, by the groups of de Meijere and recently by Armstrong.[4] Routes to analogues of belactosin A are clearly of interest, with a view to improving its weak antitumor activity. Conformationally restricted analogues of important amino acids such as glutamate or homoserine are also of general interest. The close analogy between the global energy minimum conformation of **3** (as determined by a 15°-resolution full-circle torsion-driving conformational search of all sp^3-sp^3 rotatable bonds in MacroModel[5] with the GB/SA water solvation model) and the pharmacologically relevant extended conformation of glutamate can be seen from the overlay in Figure 2. The cyclopropanol OH group is almost perfectly superimposed on the δ acid oxygen of glutamate.

In recent years, we have published a methodology for the synthesis of cyclopropanols from allylic sulfones. These

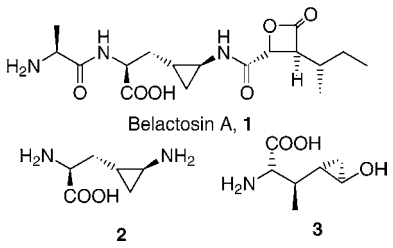

Figure 1.

[†] Lilly S.A.

(1) Salaün, J.; Baird, M. S. *Curr. Med. Chem.* **1995**, *2*, 511−542.

(2) Salaün, J. *Top. Curr. Chem.* **2000**, *207*, 1−67.

(3) (a) Asai, A.; Mizukami, T.; Yamashita, Y.; Akinaga, S.; Ikeda, S.; Kanda, Y. Eur. Patent 1166781, 2002; *Chem Abstr*. **2002**, *133*, 120677. (b) Asai, A.; Hasegawa, A.; Ochiai, K.; Yamashita, Y.; Mizukami, T. *J. Antibiot.* **2000**, *53*, 81−83

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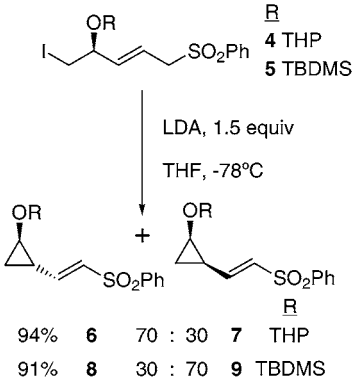
Figure 2. Overlay of Glutamic acid with **3**.

cyclopropanols also contain a vinyl sulfone unit whose reactivity could be exploited further.[6] In this paper, we describe the enantioselective synthesis of the methyl ester of **3**, which could be used as a core structure for the construction of belactosin A analogues.

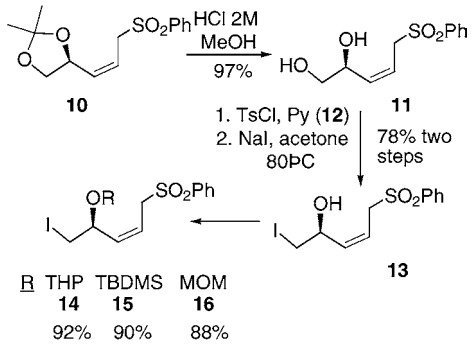
We have previously obtained cyclopropanols by treatment of allylic sulfones such as **4** or **5** with LDA, with a diastereoselectivity of 70:30 or 30:70 for the trans:cis cyclopropanols, depending on the protecting group (for example, see Scheme 1).

Scheme 1

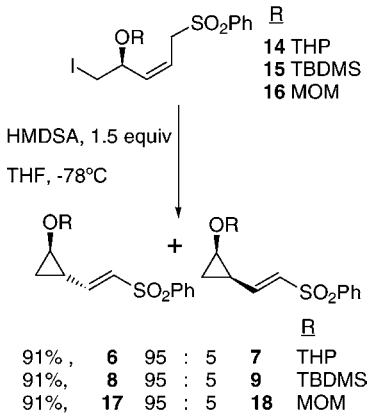


Using the same methodology used previously[7] (Scheme 2), we were able to obtain compounds **14** and **15**, which differ with respect to compounds **4** and **5** only in the stereochemistry of the allyl sulfone, and the protecting group variant **16**. Here we report that by means of this stereochemical change, in combination with a change in the base used, we were able to increase the trans/cis ratio of the product cyclopropanes to 95:5, independent of the protecting group used (Scheme 3).

Scheme 2



Scheme 3



When compounds **14**, **15** and **16** were treated under the conditions described for the cyclopropanol formation, vinyl cyclopropanols **6**, **8**, and **17**, respectively, were obtained with excellent diastereoselectivity (Scheme 3).

The stereochemistry of compound **17** was established by X-ray crystallography (Figure 3).

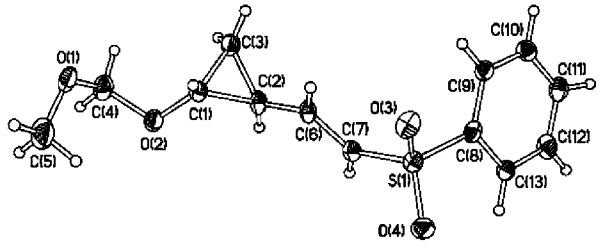


Figure 3. Single-crystal X-ray structure of **17**.

Since our initial attempts to try to understand why the stereoselectivity was so much better for the *cis*-allyl sulfone

(4) (a) Brandl, M.; Kozhushkov, S. I.; Loscha, K.; Kokoreva, O. V.; Yufit, D. S.; Howard, J. A. K.; de Meijere, A. *Synlett* **2000**, 1741−1744. (b) Larionov, O. V.; Savel'eva, T. F.; Kochetkov, K. A.; Ikonnokov, N. S.; Kozhushkov, S. I.; Yufit, D. S.; Howard, J. A. K.; Khrustalev, V. N.; Belokon, Y. N.; de Meijere, A. *Eur. J. Org. Chem.* **2003**, 869−877. (c) Armstrong, A.; Scutt, J. M. *Org. Lett.* **2003**, *5*, 2331−2334.

(5) *MacroModel v8.1.031*; Schrodinger, LLC: Portland, OR.

(6) (a) Diez, D.; García, P.; Pacheco, M. P.; Marcos, I. S.; Garrido, N. M.; Basabe, P. and Urones, J. G. *Synlett* **2002**, 355. (b) Diez, D.; García, P.; Marcos, I. S.; Garrido, N. M.; Basabe, P., Urones, J. G. *Synthesis* **2003**, 53

(7) Díez, D.; San Feliciano, S. G.; Marcos, I. S.; Basabe, P.; Garrido, N. M.; Urones, J. G. *Synthesis* **2001**, 1069.

(such as **16**) than it had been for *trans*-allyl sulfones (such as **4**) using Newman projections or Dreiding models failed to provide a convincing explanation, we used a simple molecular modeling approach to help guide us in the formulation of a hypothesis. It has been suggested[8] that there are a number of accessible structures for solvated allyl sulfone lithium species, including some in which the lithium is remote from the reacting site. The metal ion and solvation shell are thus less likely to dominate the reaction profile, justifying a highly simplified model in which the cation and solvent were ignored. Further support for this simplification came from our experiments, which showed that the stereochemical outcome of the *cis*-allyl sulfone cyclization was essentially independent of the cation. Without detailed knowledge of the solvation state and the location of the cation, the conclusions from these studies must be seen as a starting point for future, more detailed theoretical and experimental investigations, but nonetheless provide some support for an initial hypothesis as to the origin of the observed stereocontrol. We initially considered the possibility that the transition state would be starting-material-like and studied the likely conformational preferences of the anion of **16** and of the trans double-bond isomer of **16**. A grid search of the conformational energy was carried out on the anionic species using the MMFF94S force field and charge model in Sybyl.[9] The C2−C1 bond was rotated 360° in 15° increments and the C1−O bond rotated 360° in 60° increments. However, the conformational profiles of both *cis*- and *trans*-allyl sulfone anions were very similar, with the lowest-energy conformation in each case being one that would lead to the *cis*-cyclopropane, with conformations that would give rise to the *trans*-cyclopropane, higher in energy by ca. 2 kcal/mol. Simplified structures (methyl instead of phenyl, and methoxy instead of MOM) based on the local energy minima located by MMFF were subjected to geometry optimization at the ab initio HF/3-21G* level (using Spartan[10]) and showed slightly decreased energy differences but the same general trend (preference for the *cis*-cyclopropane precursor conformation of 1.56 and 0.65 kcal/mol for the cis and trans double bond, respectively, clearly not in line with observation). We therefore considered the possibility that the transition state was product-like and examined the conformations of the product cyclopropanes **17** and **18**. We constrained the C7−C6−C2−C1 torsion to the eclipsed syn and anti positions, modeling the expected initial product of the *cis*- and *trans*-allyl sulfone cyclizations, respectively. The top two structures in Figure 4 are models for product-like transition states of *trans*-allyl sulfone cyclization, while those in the lower half are models for the cyclization of the cis allyl sulfones. The structures on the left are *trans*-cyclopropanes (conformers of **17**), and those on the right are *cis*-cyclopropanes (conformers of **18**). In each case, the *trans*-cyclopropane is slightly lower in MMFF94s energy. The difference is larger for the bottom two structures in Figure 4, based on the *cis*-allyl sulfone, than for the top two structures, albeit by only

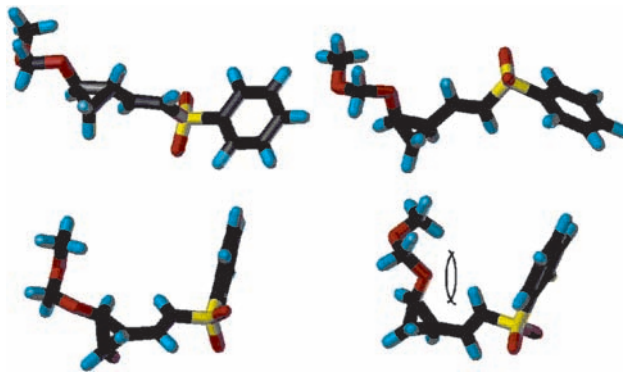


Figure 4. Models for product-like transition states for *trans*- (top) and *cis*- (bottom) allylsulfone cyclizations to *trans*- (left side) or *cis*- (right side) cyclopropanes.

0.4 kcal/mol; this is consistent with a stronger preference for *trans*-cyclopropane formation from the cis double-bond precursor than from the trans double-bond precursor. As a difference between energy differences, the 0.4 kcal/mol value should benefit from cancellation of error and hence be a useful indicator of the trend, despite its magnitude. Repetition of the calculation at the ab initio HF/6-31G* level in Spartan suggests that cyclization of the trans isomer of **16** should preferentially give rise to the *cis*-cyclopropane (difference of 0.87 kcal/mol), while cyclization of the cis compound **16** should preferentially give rise to the *trans*-cyclopropane (difference 0.93 kcal/mol); hence, the difference between energy differences at the HF/6-31G* level is widened to 1.8 kcal/mol. This appears to arise from an unfavorable interaction between the proton on the C7 carbon and the oxygen atom of the MOM group, as can be seen in the lower right structure in Figure 4. This interaction would indeed be expected to be significant in a late transition state for the cyclization of **16** to the *cis*-cyclopropane **18** but is absent for the trans product **17** or for *trans*-allyl sulfone starting materials. Thus, it seems reasonable to suggest that the stereochemical outcome of this reaction is due to a fairly late transition state in which the unfavorable C7−O interaction is avoided to give the *trans*-cyclopropane **17** as the major product.

The versatility of vinyl sulfones in organic chemistry[11] is well-known, in particular as Michael acceptors and in stabilization of an anion at the α-position.[12] These compounds seemed to us to be excellent starting materials to explore the utility of lithiated Schöllkopf's bislactim ether[13] in Michael addition with vinyl sulfones. This methodology has been widely employed in aldol reactions and Michael-type reactions with ester, nitro, α,*β*-unsaturated 2,4-pentadienoates and 1,3-butadienylphosphonates.[14]

(8) Piffl, M.; Weston, J.; Günther, W.; Anders, E. *J. Org. Chem.* **2000**, 65, 5942

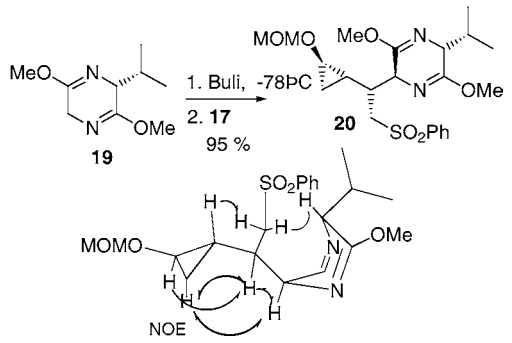
(9) *Sybyl*, version 6.9; Tripos, Inc.: St. Louis, MO.

(10) *Spartan 02 Windows;* Wavefunction, Inc.: Irvine, CA.

(11) (a) Bäckvall, J.-E.; Juntunen, S. K. *J. Org. Chem.* **1988**, *53*, 2398. (b) Fuchs, P. L.; Hentemann, M. F. *Org. Lett.* **1999**, *1*, 1355. Iradier, F.; Arrayas, R. G.; Carretero, J. C. *Org. Lett.* **2001**, *3*, 2957. (c) Padwa, A.; Murphree, S. S.; Ni, Z. J. *J. Org. Chem.* **1996**, *61*, 3829. (d) Bäckvall, J.-E.; Chinchilla, R.; Nájera, C.; Yus, M. *Chem. Rev.* **1998**, *98*, 2291.(e) Iradier, F.; Arrayas, R. G.; Carretero, J. C. *Org. Lett.* **2001**, *3*, 2957. (f) Bäckwall, J.-E.; Chinchilla, R.; Nájera, C.; Yus, M. *Chem. Rev.* **1998**, *98*, 2291

The lithium salt of **19** rapidly adds to compound **17** at low temperatures to afford the addition product **20** in excellent yield with nearly complete diastereoselectivity. This stereoselectivity could be understood by reference to transition states similar to those proposed by Schöllkopf for the addition of the lithiated bislactim ether to α,β-unsaturated ester or nitro compounds.[13,14b] The stereochemistry of the addition product **20** was established by study of the NMR spectra and NOE experiments (see Scheme 4.)

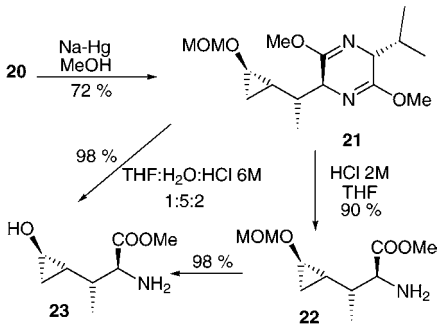
Scheme 4



Finally, deprotection first of the sulfone group (under the usual conditions) and then successive (via **22**) or one-pot hydrolysis of the protecting groups led to the cyclopropanol amino acid methyl ester **23** (Scheme 5).

In conclusion, we have obtained cyclopropanols substituted with a vinyl sulfone with high diastereoselectivity, which we attribute to a product-like transition state in which

Scheme 5



unfavorable interactions between C7 and the protected secondary alcohol are minimized. These compounds have been used for the synthesis of a chiral unnatural amino acid of restricted conformation that could be used for the synthesis of analogues of belactosin A or other peptides. The synthesis makes use of Schöllkopf lithiated bislactim ether methodology with vinyl sulfones, a methodology that has not been used before. This opens the way for the synthesis of a large variety of cyclopropanol amino acids due to the simplicity, high yield, and high diastereocontrol of the method. All compounds could be obtained in both enantiomeric forms by choosing the appropriate starting material, easily available in both enantiomeric forms.[6]

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Supporting Information Available: Experimental procedures and complete characterization for all new compounds, as well as X-ray crystalographic analysis data for **17**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) Schöllkopf, U.; Pettig, D.; Busse U. *Synthesis* **1986**, 737−740.
(14) (a) Williams, R. M. Synthesis of Optically Active α-Amino Acids. In *Tetrahedron Organic Series*; Pergamon: New York, 1989. (b) Schöllkopf, U.; Kühnle, W; Egert, E.; Dyrbusxch, M. *Angew. Chem., Int. Ed.* **1987**, *26*, 480−482. (c) Ojea, V.; Conde, S.; Ruiz, M.; Fernández, M. C.; Quintela, J. M. *Tetrahedron Lett.* **1997**, *38*, 4311−4314.