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Stereoselective Synthesis of Enamides by a Peterson Reaction Manifold

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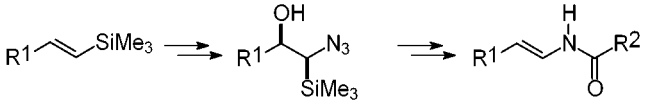
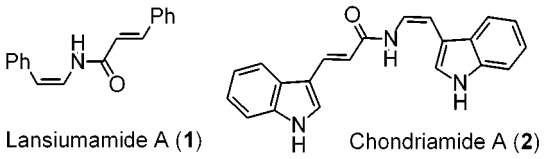
ABSTRACT



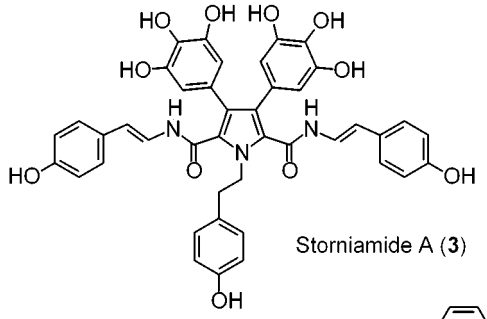
Vinylsilanes are converted into enamides by a sequence comprising epoxidation, nucleophilic ring opening of the resulting epoxysilanes with NaN_3, and reduction of the azide, followed by a "one-pot" *N*-acylation/Peterson elimination process. This method is distinguished by its wide applicability and stereoselective course.

The enamide linkage represents a fragile structural element that is prominently featured in a wide range of natural products with promising biological activities. This includes compounds as diverse as lansiumamide A (**1**),[1] the chondriamides (e.g., **2**),[2] the storniamides (e.g., **3**),[3] salicylihalamide (**4a**,**b**) and congeners,[4,5] and a host of acyclic and cyclic peptides such as **5**,[6] to mention just a few prototype examples.

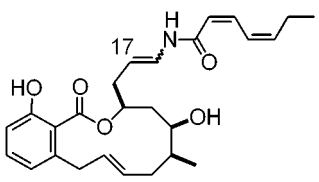


Lansiumamide A (**1**)

Chondriamide A (**2**)

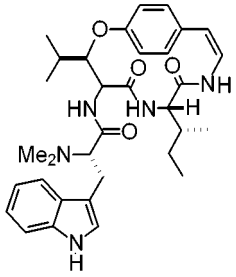


Storniamide A (**3**)



Salicylihalamide A (**4a**): 17(*E*)

Salicylihalamide B (**4b**): 17(*Z*)



Waltherine B (**5**)

Recent investigations dealing with the synthesis and biological evaluation of the potent cytotoxic agent **4** have shown that the C(17)−C(18) enamide moiety is an essential part of the pharmacophore of this lead compound.[7,8] However, they have also revealed that the formation of this entity is far from trivial.[9] Therefore, we were prompted to devise a novel and widely applicable method which provides rigorous control over the stereochemistry of the enamide

(1) (a) Isolation: Lin, J.-H. *Phytochemistry* **1989**, *28*, 621 and references therein. (b) Synthesis: Stefanuti, I.; Smith, S. A.; Taylor, R. J. K. *Tetrahedron Lett.* **2000**, *41*, 3735.

(2) (a) Palermo, J. A.; Flower, P. B.; Seldes, A. M. *Tetrahedron Lett.* **1992**, *33*, 3097. (b) Davyt, D.; Entz, W.; Fernandez, R., Mariezcurrena, R.; Mombrú, A. W.; Saldaña, J.; Domínguez, L.; Coll, J.; Manta, E. *J. Nat. Prod.* **1998**, *61*, 1560.

(3) (a) Isolation: Palermo, J. A.; Brasco, M. F. R.; Seldes, A. M. *Tetrahedron* **1996**, *52*, 2727. (b) Preparative studies: Ebel, H.; Terpin, A.; Steglich, W. *Tetrahedron Lett.* **1998**, *39*, 9165. (c) Boger, D. L.; Boyce, C. W.; Labroli, M. A.; Sehon, C. A.; Jin, Q. *J. Am. Chem. Soc.* **1999**, *121*, 54.

(4) Erickson, K. L.; Beutler, J. A.; Cardellina, J. H.; Boyd, M. R. *J. Org. Chem.* **1997**, *62*, 8188. Correction: Erickson, K. L.; Beutler, J. A.; Cardellina, J. H.; Boyd, M. R. *J. Org. Chem.* **2001**, *66*, 1532.

(5) For closely related compounds, see the following: (a) Lobatamides: McKee, T. C.; Galinis, D. L., Pannell, L. K.; Cardellina, J. H.; Laakso, J.; Ireland, C. M.; Murray, L.; Capon, R. J.; Boyd, M. R. *J. Org. Chem.* **1998**, *63*, 7805. (b) Oximidines: Kim, J. W.; Shin-ya, K.; Furihata, K.; Hayakawa, Y.; Seto, H. *J. Org. Chem.* **1999**, *64*, 153. (c) CJ-12,950 and CJ-13,357: Dekker, K. A.; Aiello, R. J.; Hirai, H.; Inagaki, T.; Sakakibara, T.; Suzuki, Y.; Thompson, J. F.; Yamauchi, Y.; Kojima, N. *J. Antibiot.* **1998**, *51*, 14. (d) Apicularens: Jansen, R.; Kunze, B.; Reichenbach, H.; Höfle, G. *Eur. J. Org. Chem.* **2000**, 913.

(6) Morel, A. F.; Gehrke, I. T. S.; Mostardeiro, M. A.; Ethur, E. M.; Zanatta, N.; Machado, E. C. S. *Phytochemistry* **1999**, *51*, 473.

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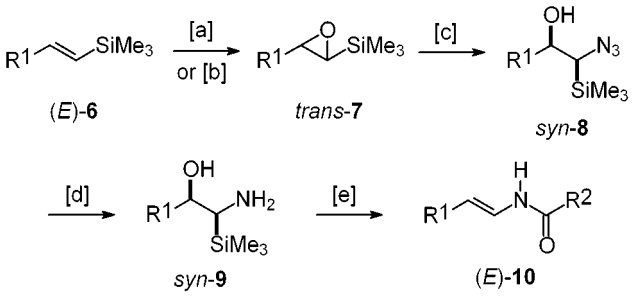
double bond. Outlined below is the concept of our synthesis route together with a series of model studies.

In view of the inherent lability of enamides toward acid-catalyzed hydrolysis, we pursued a strategy which allows for the stereoselective formation of the double bond under mild, aprotic, and basic conditions (Schemes 1 and 2). The

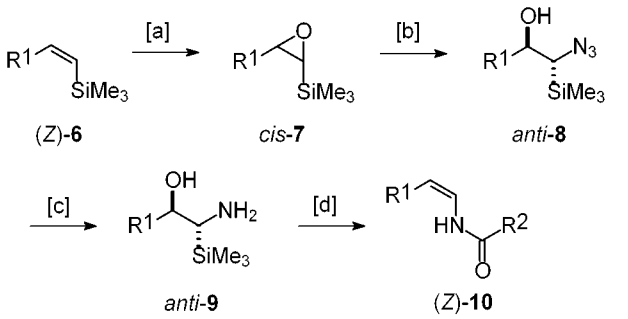
Scheme 1. Stereoselective Conversion of (*E*)-Alkenylsilanes into (*E*)-Enamides[a]



[a] [a] *m*-CPBA, Na_2HPO_4, CH_2Cl_2, 60% (R^1 = *n*-pentyl); [b] dimethyldioxirane, acetone/CH_2Cl_2, 89% (R^1 = Ph); [c] NaN_3, NH_4Cl, MeOH/H_2O, 75% (R^1 = *n*-pentyl); 68% (R^1 = Ph); [d] $LiAlH_4$, Et_2O, 93% (R^1 = *n*-pentyl); 97% (R^1 = Ph); [e] (i) R^2COCl, THF, NEt_3; (ii) KOtBu, −35 °C → rt, see Table 1.

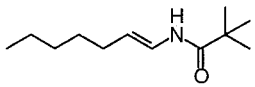
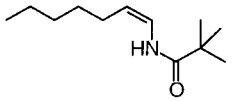
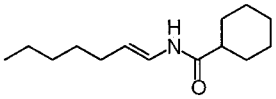
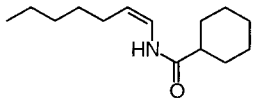
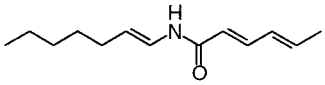
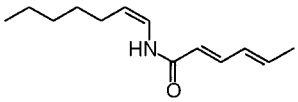
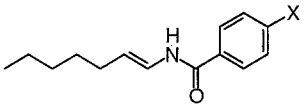
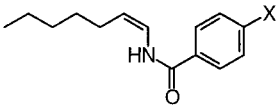
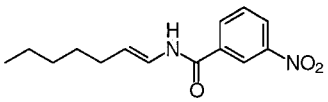
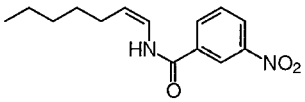
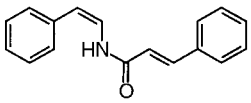
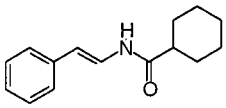
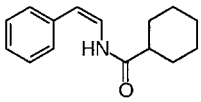
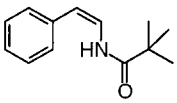
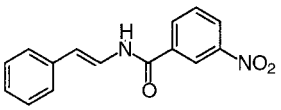
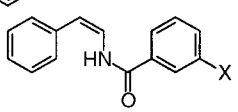
famous Peterson elimination[10−12] seems to meet these stringent criteria. Thus, we envisaged the use of epoxysilanes as starting materials which can be prepared by a variety of efficient methods.[11,13] Specifically, compounds *trans*-**7** and *cis*-**7** used as model substrates are conveniently obtained by reaction of vinylsilanes (*E*)-**6** or (*Z*)-**6**, respectively,[14] with *m*-chloroperbenzoic acid or dimethyldioxirane.[15] Silicon-directed epoxide ring opening with NaN_3 in a buffered medium[16] furnishes products **8**, which can be selectively reduced to the corresponding amino alcohols **9** in many different ways.[17] For the sake of convenience, we took recourse to $LiAlH_4$ or hydrogenolysis during this investigation.

Scheme 2. Stereoselective Conversion of (*Z*)-Alkenylsilanes into (*Z*)-Enamides[a]



[a] [a] *m*-CPBA, Na_2HPO_4, CH_2Cl_2, 90% (R^1 = *n*-pentyl); 81% (R^1 = Ph); [b] NaN_3, NH_4Cl, MeOH/H_2O, 88% (R^1 = *n*-pentyl); 89% (R^1 = Ph); [c] $LiAlH_4$, Et_2O, quantitative (R^1 = *n*-pentyl); 73% (R^1 = Ph); [d] (i) R^2COCl, THF, NEt_3; (ii) KOtBu, −35 °C → rt, see Table 1.

Table 1. Stereoselective Synthesis of (*E*)- or (*Z*)-Configured Enamides. The Yield Refers to Analytically Pure Material Obtained over Two Steps (*N*-Acylation/Peterson Elimination), cf. Text

substrate	product	yield (%)
syn-**9a**		79
anti-**9a**		57
syn-**9a**		56
anti-**9a**		74
syn-**9a**		75
anti-**9a**		69
syn-**9a**		78 (X = H) 89 (X=OMe)
anti-**9a**		66 (X = H) 77 (X=OMe)
syn-**9a**		68
anti-**9a**		71
anti-**9b**		57
syn-**9b**		62
anti-**9b**		85
anti-**9b**		60
syn-**9b**		64
anti-**9b**		61 (X = H) 60 (X=NO_2)

The key steps of our new enamide synthesis can either be carried out in a consecutive manner or, preferentially, in "one pot" (for experimental details, see the Supporting Information). Thus, *N*-acylation of amine *syn*-**9** under standard conditions followed by addition of KOtBu to the solution of the resulting amide at low temperature affords the desired enamides (*E*)-**10** in virtually quantitative yield; the crude material is usually pure enough for further use (>95% by ^{1}H NMR). Analogously, *anti*-**9** is converted into the diastereomeric products (*Z*)-**10**. This includes a synthesis of lansiumamide A (**1**, Table 1, entry 11) which compares favorably with a previous approach to this natural product reported in the literature.[1b] Analytically pure samples are obtained by flash chromatography; although care was taken to minimize the amount of adsorbent used as well as the time of exposure, some loss of material can hardly be avoided due to the lability of some of the products. This explains why the isolated yields shown in Table 1 are only in the range of 56−89%. It was noticed that the hydrolysis is particularly facile for (*Z*)-configured enamides. Most important, however, is the fact that all products are obtained as single diastereomers. Thus, the configuration of the starting material is transferred in a predictable manner and with high integrity into the final product. This rigorously stereoselective and controlable course distinguishes the protocol outlined above from many of the alternative methods previously described in the literature. Further work aimed at the implementation of this new strategy into the total synthesis of bioactive target molecules[18] is currently underway and will be reported soon.

Acknowledgment. Generous financial support by the Deutsche Forschungsgemeinschaft (Leibniz award to A.F.) and the Fonds der Chemischen Industrie is gratefully acknowledged.

Supporting Information Available: Representative procedures as well as analytical and spectroscopic data of all new compounds. This material is available free of charge via the Internet at http:pubs.acs.org.

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(10) For pertinent reviews see: (a) Ager, D. J. *Org. React.* **1990**, *38*, 1. (b) Ager, D. J. *Synthesis* **1984**, 384.

(11) Brook, M. A. *Silicon in Organic, Organometallic and Polymer Chemistry*; Wiley: New York, 2000.

(12) It is well established that a *syn*-elimination of the -OH and -$SiMe_3$ group takes place in base-induced Peterson reactions, cf. (a) Hudrlick, P. F.; Peterson, D. *J. Am. Chem. Soc.* **1975**, *97*, 1464. (b) Hudrlick, P. F.; Peterson, D.; Rona, R. J. *J. Org. Chem.* **1975**, *40*, 2263.

(13) The use of epoxysilanes as substrates for the synthesis of enamides has precedence in the two examples reported in ref 9c. In these cases the epoxide ring is opened by acetonitrile used as solvent which clearly limits the scope of the method.

(14) The vinylsilanes used have been prepared according to the following references. (a) (*E*)-**6a** (R^1 = *n*-pentyl): Koumaglo, K.; Chan, T. H. *Tetrahedron Lett.* **1984**, *25*, 717. (b) (*Z*)-**6a** (R^1 = *n*-pentyl): Page, P. C. B.; Rosenthal, S. *Tetrahedron* **1990**, *46*, 2573. (c) (*Z*)-**6b** (R^1 = Ph): Barton, T.; Lin, J.; Ijadi-Maghsoodi, S.; Power, M. D.; Zhang, X.; Ma, Z.; Shimizu, H.; Gordon, M. S. *J. Am. Chem. Soc.* **1995**, *117*, 11695. (d) (*E*)-**6b** (R^1 = Ph): Jeffery, T. *Tetrahedron Lett.* **1999**, *40*, 1673.

(15) (a) Soderquist, J. A.; Santiago, B. *Tetrahedron Lett.* **1989**, *30*, 5693. (b) Alexakis, A.; Jachiet, D. *Tetrahedron* **1989**, *45*, 381.

(16) Chakraborty, T. K.; Reddy, G. V. *Tetrahedron Lett.* **1990**, *31*, 1335.

(17) For a compilation see: Larock, R. C. *Synthetic Organic Methodology: Comprehensive Organic Transformations. A Guide to Functional Group Preparations*; VCH: Weinheim, 1989.

(18) Fürstner, A. *Synlett* **1999**, 1523.