Natural Product Synthesis

DOI: 10.1002/ange.200702637

An Alkyne Strategy for the Asymmetric Synthesis of Natural Products: Application to (+)-Spirolaxine Methyl Ether**

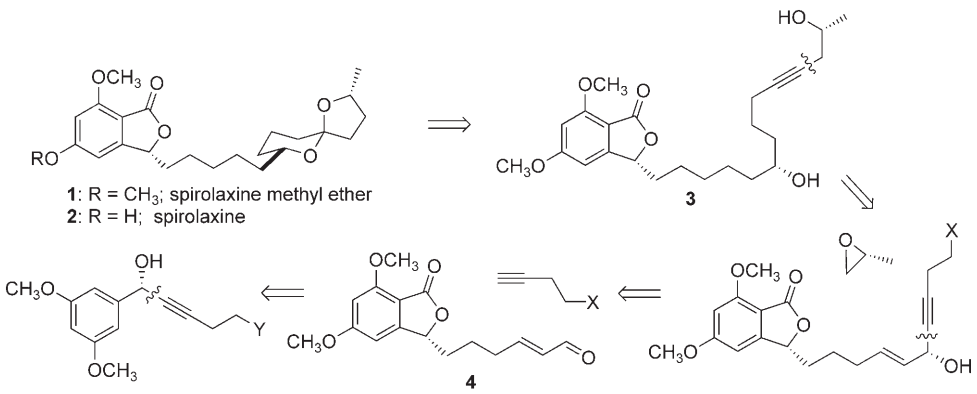
Barry M. Trost and Andrew H. Weiss*

The ketone is traditionally regarded as the most useful and important functional group in organic synthesis.[1] The defining feature of the reactivity of a ketone is its dual character as both an inherent electrophile (at the carbonyl carbon atom) and susceptibility to be rendered nucleophilic by deprotonation (at the α carbon atom). The alkyne functional group possesses the same bifunctional versatility. The acidity of a terminal alkyne facilitates its use as a nucleophile (equilibrium pK_a in dimethyl sulfoxide:[2] phenyl acetylene $pK_a = 28.7$, cyclohexanone $pK_a = 26.4$) when reacting with carbonyls, epoxides, and alkylating agents. While not inherently electrophilic, alkynes can be chemoselectively activated towards nucleophiles by complexation with a transition metal.[3] For this reason, alkynes are effective ketone surrogates in the context of total synthesis.[4]

Acetylenes offer many additional advantages over ketones as synthetic intermediates. Since alkynes are inert to a wide range of conditions used in standard organic transformations, the use of protecting groups can often be avoided. Acetylenes can also be employed in chemoselective carbon–carbon bond forming reactions that are unavailable to ketones such as [2+2+2] cycloadditions,[5] alkene–alkyne coupling reactions,[6] and reductive coupling reactions.[7]

To showcase the synthetic advantage of alkynes, we devised a synthetic strategy toward the (+)-spirolaxine methyl ether (**1**). The spirolaxines were first isolated from the white-rot fungus *Sporotrichum laxum*, and tested for plant-growth inhibition.[8] Since their initial isolation, the bioactivity of the spirolaxines has been studied for several therapeutic manifolds, including cholesterol-lowering activity[9] and cytotoxicity against endothelial cells and several tumor cell lines (LoVo, HL60).[10] One of the most striking properties of **1** is its potent activity against *Helicobacter pylori* and complete lack of antibacterial activity against a panel of different microorganisms.[11]

The interesting biological activity and structure has also attracted others to spirolaxine methyl ether (**1**), which has resulted in three total syntheses.[12] The molecule is comprised of two key portions: a phthalide and a spiroketal, linked by a five carbon atom chain. Retrosynthetically we envisioned spiroketal formation through a transition-metal-catalyzed cyclization of alkyne diol **3** (Scheme 1).



Scheme 1. Retrosynthetic analysis.

We then envisioned a series of three alkyne additions to stitch together the carbon framework while establishing both the absolute and relative stereochemistry. The stereochemistry of the spiroketal fragment could be derived from (*R*)-(+)-propylene oxide and a catalyst-controlled diastereoselective alkyne addition to the α,β-unsaturated aldehyde **4**. The phthalide portion would be accessed by an enantioselective alkynylation of 3,5-dimethoxybenzaldehyde. Thus, stereocontrolled alkyne additions to unsaturated aldehydes were considered to be key to access both subunits.

The enantioselective addition of terminal alkynes to aldehydes is an active field of research and many efficient and complimentary catalyst systems have been designed.[13] Our group reported the alkynylation of aromatic and unsaturated aldehydes[13h] catalyzed by the commercially available ProPhenol ligand (**5**). Our alkynylation demon-

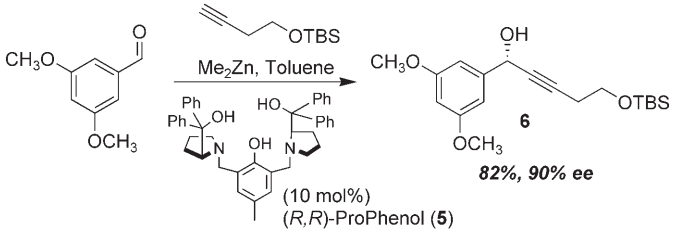
[*] Prof. B. M. Trost, A. H. Weiss
Department of Chemistry
Stanford University
Stanford, CA 94305-5080 (USA)
Fax: (+1) 650-725-0259
E-mail: bmtrost@stanford.edu

[**] We thank NIH (GM 13598) and the National Science Foundation for the generous support of our programs. A.H.W. thanks GlaxoSmithKline (ACS Division of Organic Chemistry Fellowship) and Bristol–Myers Squibb (for a graduate fellowship). Mass spectra were provided by the Mass Spectrometry Regional Center of the University of California, San Francisco, which is supported by the NIH Division of Research Resources. Palladium salts were generously supplied by Johnson–Matthey.

Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

strates broad scope with respect to both the aldehyde and the alkyne, thus giving access to adducts that present challenges to other alkynylation procedures. We questioned whether we could use this empowering method twice in our route to build up the carbon framework while controlling the stereochemistry on each side of the molecule.

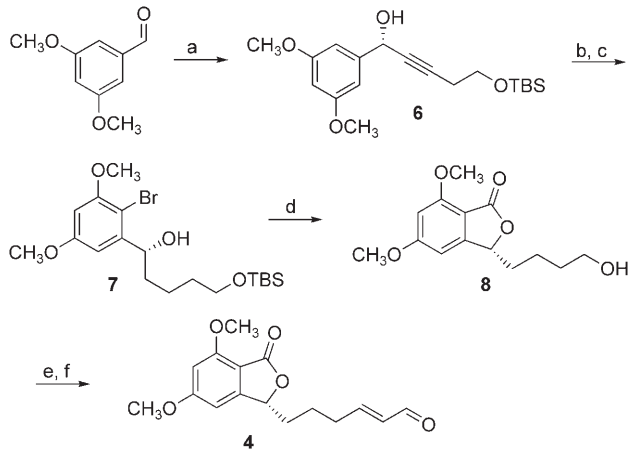
In a forward sense, the ProPhenol-catalyzed addition of 4-(*tert*-butyldimethylsilyloxy)-1-butyne to 3,5-dimethoxybenzaldehyde reproducibly led to high yield and enantiomeric excess of the desired propargylic alcohol **6** (82% yield, 89–90% *ee*) on a 6.5 mmol scale (Scheme 2). All of these reagents were commercially available and used directly. The absolute configuration was assigned by analogy to other aromatic alkynylations with the ProPhenol catalyst.[13h]



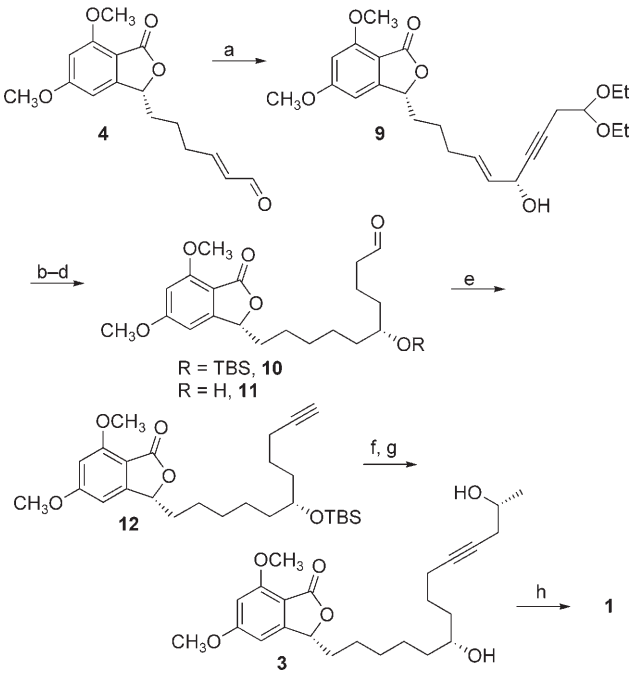
Scheme 2. ProPhenol-catalyzed enantioselective alkynylation. TBS = *tert*-butyldimethylsilyl.

With direct access to homochiral propargylic alcohol **6**, our attention turned to the elaboration of phthalide **4** (Scheme 3). Acetylenes, although at the ketone oxidation state, are excellent synthons for alkanes ($-CH_2CH_2R$), *Z* olefins (through Lindlar reduction[14]), and *E* olefins (by dissolving metal reductions[15] or *trans*-hydrosilylation chemistry[16]). Mild hydrogenation of alkyne **6** with the Adams catalyst[17] in ethyl acetate furnished the saturated alkane without reduction of the benzylic alcohol observed with Pd/C (Scheme 3). Directed *ortho*-lithiation of the benzyl alcohol and subsequent trapping with CO_2 would be the most direct route to phthalide **8**. Unfortunately, this lithiation suffered from poor regioselectivity, a result also observed[18] with similar substrates. In stark contrast, bromination proved to be an extremely regioselective route to activation of the dimethoxy aromatic ring, and provided phthalide precursor **7** in nearly quantitative yield. From bromo alcohol **7**, there were two routes to the desired phthalide: Pd-catalyzed carbonylation[19] or lithium-halogen exchange with CO_2 trapping. Pd-catalyzed carbonylation to access phthalide **8** was largely unsuccessful,[20] with only trace product formed. Our initial examination of the anionic route was initially frustrated by debrominated product (presumably from rapid lithium-halogen exchange and internal proton transfer).[18] This setback could be mitigated by treating **7** with *n*BuLi (2.2 equiv) at −78 °C for only one minute, then rapidly flushing the reaction with CO_2 gas to trap the aryl lithium species. After acidic workup, phthalide **8** was isolated with concomitant silyl group cleavage in high yield (90%). Oxidation of the primary alcohol **8** and homologation using Wittig olefination gave access to enal **4**.

With the phthalide portion complete, our attention turned to the synthesis of the spiroketal portion of the molecule. A second ProPhenol-catalyzed asymmetric alkynylation was employed to set the stereochemistry of the distal stereogenic center and to construct the carbon skeleton (Scheme 4). Catalyst-controlled diastereoselective alkynylation of enal **4**



Scheme 3. Phthalide synthesis. a) (*R,R*)-**5** (10 mol%), Me_2Zn, 4-(*tert*-butyldimethylsilyloxy)-1-butyne, toluene, 82%, 90% *ee* (determined by HPLC on a chiral stationary phase); b) H_2, PtO_2, EtOAc, quant.; c) NBS, $CHCl_3$, 99%; d) *n*BuLi (1 min), THF, −78 °C then CO_2, HCl/H_2O, 90%; e) TEMPO (5 mol%), bisacetoxyiodobenzene, 84%; f) (triphenylphosphoranylidene)acetaldehyde, benzene, 80 °C, 56%. NBS = *N*-bromosuccinimide, TEMPO = 2,2,6,6-tetramethylpiperidin-1-yloxyl.



Scheme 4. Spiroketal synthesis. a) 4,4-diethoxybut-1-yne, Me_2Zn, (*S,S*)-**5** (10 mol%), toluene, 52%, 5:1 d.r. (d.r. and absolute configuration determined by formation of methyl mandelate); b) TBSCl, imidazole, CH_2Cl_2, 71%; c) H_2, PtO_2, 91%; d) PPTS, wet acetone, 98%; e) Ohira–Bestmann, K_2CO_3, MeOH, 75%; f) *n*BuLi, $BF_3{\cdot}Et_2O$, (*R*)-(+)-propylene oxide. g) HCl/H_2O, 51% (2 steps); h) $[PdCl_2(PhCN)_2]$, THF/CH_3CN 3:1, 79%. PPTS = pyridinium toluene-*para*-sulfonate.

with 4,4-diethoxybut-1-yne[21] gave access to the desired propargylic alcohol **9** without disturbing the relatively sensitive phthalide group. The diastereomeric ratio and absolute configuration of this new stereocenter were determined by formation of the methyl mandelate ester (see the Supporting Information). Our initial plan was to forego the TBS group (Scheme 4, omit step b) to access the hydroxy aldehyde **11** (in the hemiacetal tautomer). Subjection of **11** to TMS-diazomethane and subsequent trapping with propylene oxide did not give alkyne diol **3** directly as planned because of a competitive destruction of the phthalide lactone with TMS-diazomethane. For this reason, alcohol **9** was silylated, followed by global reduction to the fully saturated chain. Acid hydrolysis of the diethyl acetal furnished the silyl-protected alkoxy aldehyde **10**. Homologation of aldehyde **10** to the terminal alkyne without destruction of the phthalide was accomplish by the mild Ohira–Bestmann[22] alkynylation.

Spiroketal precursor **3** was accessed in two steps from alkyne **12**. Addition of the alkyne to *R*-(+)-propylene oxide assisted by a Lewis acid gave the corresponding homopropargylic alcohol. Subsequent treatment with HCl effectively removed the TBS group to provide diol **3**.

In natural product synthesis, spiroketals are most commonly accessed by the alkoxylation of a ketone with pendant alcohols. While this method is generally effective (and has been used in all of the previous syntheses of spirolaxine), the ketone diol precursor comes with the inherent chemoselectivity issues associated with ketones. A complimentary alkyne diol precursor (such as **3**) would be inert to many of the standard synthetic operations that would be incompatible with a ketone. This type of spiroketalization of an alkyne was first demonstrated by Utimoto.[23] Since its discovery, it has been relatively underused in total synthesis[24] and methodological exploration.[25] We carried out the spiroketalization of **3** promoted by $[PdCl_2(PhCN)_2]$ to give (+)-spirolaxine methyl ether (**1**) in 79% yield. All spectroscopic data were in agreement with the reported data.[8,12]

In conclusion, we have synthesized (+)-spirolaxine methyl ether in 13 total steps using an alkyne-based strategy. The stereochemistry in both the phthalide portion and the spiroketal portion were established by ProPhenol catalyst-controlled asymmetric alkynylation chemistry. The carbon framework was constructed using terminal alkynes as nucleophiles, and the spiroketal was formed using an internal alkyne as an electrophilic ketone surrogate. This type of alkyne strategy will help alleviate chemoselectivity issues of ketones, and should be widely applicable to complex natural product syntheses.

Received: June 15, 2007
Published online: August 23, 2007

Keywords: alkynes · asymmetric synthesis · natural products · spiro compounds · total synthesis

[1] In regard to the ketone: "No other functional group can rival its versatility and utility." See: P. J. Kocienski, *Protecting Groups*, Thieme, Stuttgart, **2005**.
[2] a) J. H. Babler, V. P. Liptak, N. Phan, *J. Org. Chem.* **1996**, *61*, 416; b) F. G. Bordwell, *Acc. Chem. Res.* **1988**, *21*, 456.
[3] *Modern Acetylene Chemistry* (Eds.: P. J. Stang, F. Diederich), VCH, Weinheim, **1995**.
[4] Alkynes can readily be converted into ketones; see: R. C. Larock, *Comprehensive Organic Transformations*, VCH, New York, NY, **1999**.
[5] For selected reviews, see: a) K. P. C. Vollhardt, *Acc. Chem. Res.* **1977**, *10*, 1; b) M. Lautens, W. Klute, W. Tam, *Chem. Rev.* **1996**, *96*, 49; c) S. Saito, Y. Yamamoto, *Chem. Rev.* **2000**, *100*, 2901.
[6] For selected reviews, see: a) B. M. Trost, M. J. Krische, *Synlett* **1998**, 1; b) B. M. Trost, F. D. Toste, A. B. Pinkerton, *Chem. Rev.* **2001**, *101*, 2067.
[7] a) H.-Y. Jang, M. J. Krische, *Acc. Chem. Res.* **2004**, *37*, 653; b) J. Montgomery, *Acc. Chem. Res.* **2000**, *33*, 467.
[8] a) A. Arnone, G. Assante, G. Nasini, O. Vajna de Pava, *Phytochemistry* **1990**, *29*, 613; b) M. A. Gaudliana, L. H. Huang, T. Kaneko, P. C. Watts, PCT Int. Appl. W0 9605204, **1996**; c) T. Adachi, I. Takagi, K. Kondo, A. Kawashima, A. Kobayashi, I. Taneoka, S. Morimoto, B. M. Hi, Z. Chen, PCT Int. Appl. W0 9610020, **1996**.
[9] M. J. Blaser, *Clin. Infect. Dis.* **1992**, *15*, 386.
[10] A. Bava, M. Clericuzio, G. Giannini, L. Malpezzi, S. V. Meille, G. Nasini, *Eur. J. Org. Chem.* **2005**, 2292.
[11] K. A. Dekker, T. Inagaki, T. D. Gootz, K. Kanede, E. Nomura, T. Sakakibara, S. Sakemi, Y. Sugie, Y. Yamauchi, N. Yoshikawa, N. Kojima, *J. Antibiot.* **1997**, *50*, 833.
[12] a) J. E. Robinson, M. A. Brimble, *Chem. Commun.* **2005**, 1560; b) R. Nannei, S. Dallavalle, L. Merlini, A. Bava, G. Nasini, *J. Org. Chem.* **2006**, *71*, 6277; c) K. A. Keaton, A. J. Phillips, *Org. Lett.* **2007**, *9*, 2717.
[13] a) S. Niwa, K. Soai, *J. Chem. Soc. Perkin Trans. 1* **1990**, 937; b) G. M. R. Tombo, E. Didier, B. Loubinoux, *Synlett* **1990**, 547; c) N. K. Anand, E. M. Carreira, *J. Am. Chem. Soc.* **2001**, *123*, 9687; d) G. Lu, X. Li, W. L. Chan, A. S. C. Chan, *Chem. Commun.* **2002**, 172; e) G. Gao, D. Moore, R.-G. Xie, L. Pu, *Org. Lett.* **2002**, *4*, 4143; f) L. Pu, *Tetrahedron* **2003**, *59*, 9873; g) L. Pu, H.-B. Yu, *Chem. Rev.* **2001**, *101*, 757; h) B. M. Trost, A. H. Weiss, A. J. von Wangelin, *J. Am. Chem. Soc.* **2006**, *128*, 8; i) R. Takita, K. Yakura, T. Ohshima, M. Shibasaki, *J. Am. Chem. Soc.* **2005**, *127*, 13760; j) G. Gao, Q. Wang, X.-Q. Yu, R.-G. Xie, L. Pu, *Angew. Chem.* **2006**, *118*, 128; *Angew. Chem. Int. Ed.* **2006**, *45*, 122.
[14] H. Lindlar, *Helv. Chim. Acta* **1952**, *35*, 446.
[15] For a review, see: H. O. House, *Modern Synthetic Reactions*, 2nd ed., W. A. Benjamin, Menlo Park, CA, **1972**.
[16] Recent review: B. M. Trost, Z. T. Ball, *Synthesis* **2005**, 853.
[17] V. Voorhees, R. Adams, *J. Am. Chem. Soc.* **1922**, *44*, 1397.
[18] K. Orito, M. Miyazawa, H. Suginome, *Tetrahedron* **1995**, *51*, 2489.
[19] A. Cowell, J. K. Stille, *J. Am. Chem. Soc.* **1980**, *102*, 4193.
[20] P. D. Noire, R. W. Franck, *Synthesis* **1980**, 882.
[21] A. Stoller, C. Mioskowski, C. Sepulchre, F. Bellamy, *Tetrahedron Lett.* **1990**, *31*, 361.
[22] a) S. Ohira, *Synth. Commun.* **1989**, *19*, 561; b) G. J. Roth, L. Bernd, S. G. Müller, H. J. Bestmann, *Synthesis* **2004**, 59.
[23] K. Utimoto, *Pure Appl. Chem.* **1983**, *55*, 1845.
[24] B. M. Trost, D. B. Horne, M. J. Woltering, *Angew. Chem.* **2003**, *115*, 6169; *Angew. Chem. Int. Ed.* **2003**, *42*, 5987.
[25] B. Liu, J. K. De Brabander, *Org. Lett.* **2006**, *8*, 4907.

