ORGANIC LETTERS

2006
Vol. 8, No. 20
4461−4464

Catalytic Enantioselective Synthesis of Adociacetylene B

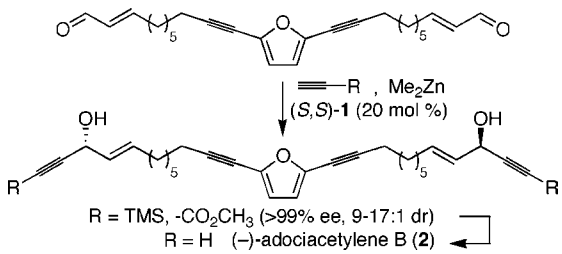
Barry M. Trost* and Andrew H. Weiss

Department of Chemistry, Stanford University, Stanford, California 94305-5080

bmtrost@stanford.edu

Received June 27, 2006

ABSTRACT



A catalytic enantioselective total synthesis of adociacetylene B (2) in five steps is reported. The efficiency of this synthesis was enabled by an asymmetric zinc alkynylation catalyzed by the proline-derived ligand (1).

We recently reported a catalytic enantioselective alkynylation of unsaturated aldehydes using our proline-derived ligand **1**.[1,2] Because of the wide generality of the terminal alkyne and tolerance of varied substitution patterns of the unsaturated aldehyde, this method gives facile access to a wide variety of highly enantioenriched propargylic alcohols. The synthetic utility of the propargylic alcohols formed by these alkynylations is demonstrated not only by their facile conversion to a variety of functional groups[3] but also directly by their presence in several natural products.[4] In the course of these studies, we developed an efficient method for the utilization of the anion of methyl propiolate as a synthon for an ethynyl anion.

The adociacetylene family of polyacetylenic natural products recently isolated from an Okinawan marine sponge *Adocia* sp. exhibits a range of biological activities from antibiotic to inhibition of the reverse transcriptase of HIV.[5] Petrosynol (**3**) (Figure 1), a member of this family that was

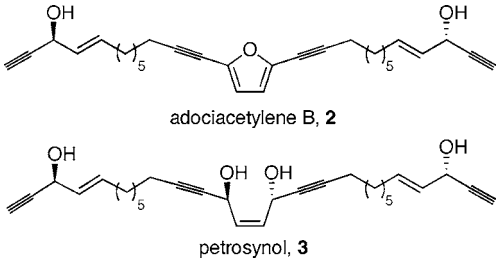


Figure 1. Polyacetylenic natural products.

previously isolated from *Petrosia* sp.,[6] showed moderate inhibition of neutrophil leukocyte adhesion to tumor necrosis factor-α endothelial cells (1μg/mL) and moderate inhibition of HIV-1 reverse transcriptase (1−6 μM).[5,7] The absolute

(1) Trost, B. M.; Weiss, A. H.; von Wangelin, A. J. *J. Am. Chem. Soc.* **2006**, *128*, 8.

(2) For leading references, see: (a) Niwa, S.; Soai, K. *J. Chem. Soc., Perkin Trans. 1* **1990**, 937. (b) Tombo, G. M. R.; Didier, E.; Loubinoux, B. *Synlett* **1990**, 547. (c) Anand, N. K.; Carreira, E. M. *J. Am. Chem. Soc.* **2001**, *123*, 9687. (d) Lu, G.; Li, X.; Chan, W. L.; Chan, A. S. C. *J. Chem. Soc., Chem. Commun.* **2002**, 172. (e) Gao, G.; Moore, D.; Xie, R.-G.; Pu, L. *Org. Lett.* **2002**, *4*, 4143. For recent reviews, see: (f) Pu, L. *Tetrahedron* **2003**, *59*, 9873. (g) Pu, L.; Yu, H. B. *Chem. Rev.* **2001**, *101*, 757. For recent advances, see: (h) Gao, G.; Wang, Q.; Yu, X.-Q.; Xie, R.-G.; Pu, L. *Angew. Chem., Int. Ed.* **2006**, *45*, 122.

(3) *Modern Acetylene Chemistry*; Stang, P. J., Diederich, F., Eds.; VCH: Weinheim, Germany, 1995.

(4) For a review, see: Shi Shun, A. L. K.; Tykwinski, R. R. *Angew. Chem., Int. Ed.* **2006**, *45*, 1034 and references therein.

(5) Kobayashi, M.; Mahmud, T.; Tajima, H.; Wang, W.; Aoki, S.; Nakagawa, S.; Mayumi, T.; Titagawa, I. *Chem. Pharm. Bull.* **1996**, *44*, 720.

(6) Fusetani, N.; Sugano, M.; Matsunaga, S.; Hashimoto, K. *Tetrahedron Lett.* **1983**, *28*, 1377.

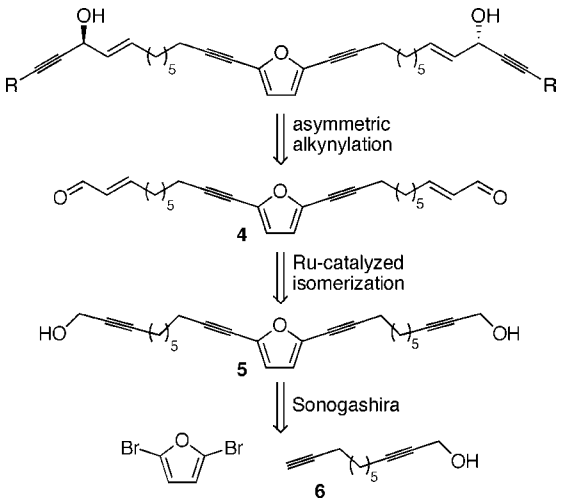
10.1021/ol0615836 CCC: $33.50
Published on Web 08/29/2006

stereochemistry of the entire family is identical and was elucidated first by the circular dichroic allylic benzoate method[8] and confirmed by NMR analysis of the Mosher esters.[5,9] Through the course of isolation and NMR studies, it was shown that petrosynol in $CDCl_3$ gradually oxidized to adociacetylene B (**2**) over a period of 40 days. This led to the hypothesis that adociacetylenes A−D are all oxidative products of petrosynol (**3**).[5] The potential of biological applications and the extremely low isolation yield (0.06%) make adociacetylene B an interesting synthetic target.

Although adociacetylene B has been synthesized twice,[10,11] neither of these routes employed catalytic enantioselective methods to form the two stereogenic centers. The Garcia group's synthesis[10] culminated in a stoichiometric reduction of the TMS-protected diynone of adociacetylene B with a chiral oxazaborolidine in low yield. To avoid the low chemoselectivity observed in the ynone reduction, the Gung group attempted the use of Carreira's asymmetric alkyne addition[12] with α,β-unsaturated dialdehyde **4**. This method did not afford the expected diol adduct with 3 equiv of the alkynylzinc−ephedrine complex. Because of the failure of the asymmetric alkynylation, the authors turned to the alkynylation of dialdehyde **4** with ethynyl Grignard to obtain a mixture of the meso and racemic adociacetylene. This mixture was resolved enzymatically to yield optically active (−)-adociacetylene B (**2**) in 22% yield.

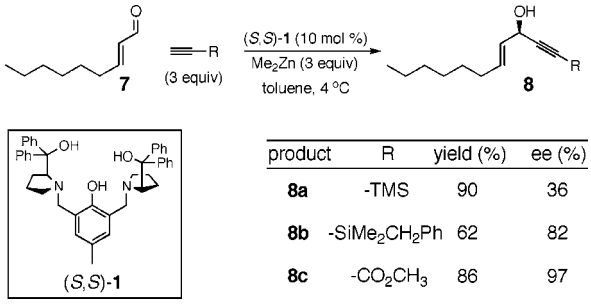
Successful asymmetric alkynylation of dialdehyde **4** would lead to an extremely efficient synthesis, making adociacetylene B an important scaffold to evaluate the utility of our alkynylation. The catalytic asymmetric alkynylation developed in our laboratory exhibited excellent generality with respect to the alkyne and was envisioned to alkynylate dialdehyde **4** with 2 equiv of a protected ethyne (Scheme 1). This type of one-pot dialkynylation has not been

Scheme 1. Retrosynthetic Analysis



attempted with our system and poses potential complications. Although relatively distal, the second addition opens the possibility of substrate control. Moreover, each enal is β-substituted with no branching at the γ position, a substitution pattern that leads to an uncharacteristically low ee with silyl-protected alkynes (Scheme 2). To efficiently access

Scheme 2. Alkynylation of Nonenal[1]



product	R	yield (%)	ee (%)
8a	-TMS	90	36
8b	$-SiMe_2CH_2Ph$	62	82
8c	$-CO_2CH_3$	86	97

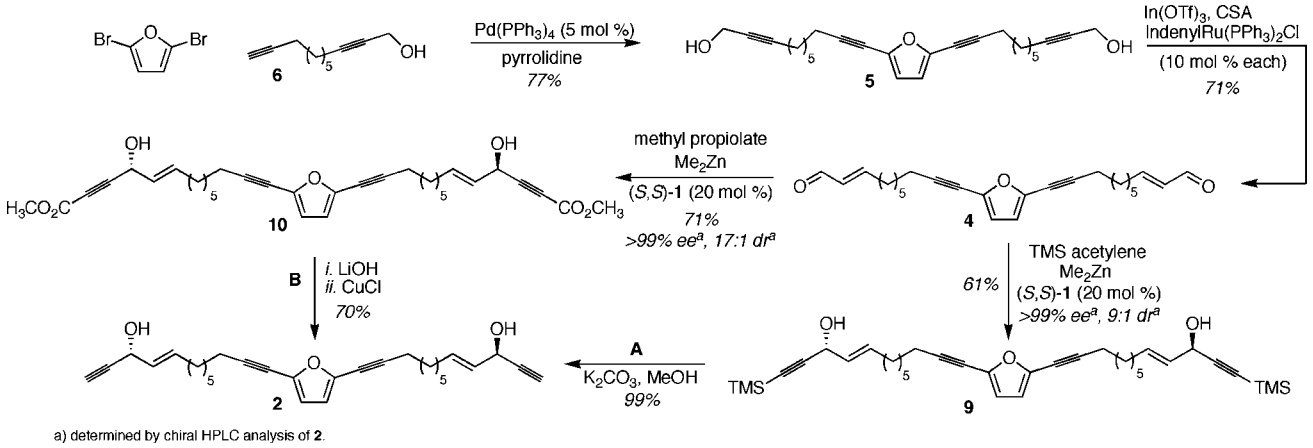
aldehyde **4** for this transformation, we envisioned the Ru-catalyzed redox isomerization of bispropargylic alcohol **5**.[13] This atom-economic isomerization would obviate the need for protecting groups and multiple oxidation and reduction steps necessary to make dialdehyde **4** via conventional olefination chemistry. At the outset, it was not known if this chemistry would tolerate both the electron-rich furan and the additional internal alkynes present.

Our synthesis (Scheme 3) began with the monoalkylation of 1,9-decadiyne with paraformaldehyde to provide known diyne **6**.[14] Copperless−Sonogashira coupling in deoxygenated pyrrolidine (Ar bubbling) using freshly distilled commercially available 2,5-dibromofuran afforded bispropargylic alcohol **5** cleanly (77% with 5 mol % of $Pd(PPh_3)_4$).[15]

Bispropargylic alcohol **5** was isomerized to dialdehyde **4** according to our published procedure[13] with 5 mol % of catalyst in 64% yield after 1 h. Although starting material still remained, longer reaction times led to lower overall yield due to decomposition. Optimal yields were obtained with increased catalyst loading (10 mol %), and dialdehyde **4** was isolated in 71% yield after 1 h. Alkynylation of dialdehyde **4** with trimethylsilyl acetylene according to the previously optimized conditions (3 equiv of Me_2Zn/TMS acetylene, 10 mol % of **1**) yielded significant amounts of starting material and monoalkynylated product, even after extended reaction times (3 days). However, doubling of the reagents and

(7) Isaacs, S.; Tashman, Y.; Loya, S.; Hizi, A.; Loya, Y. *Tetrahedron* **1993**, *49*, 10435.
(8) Fusetani, N.; Shiragaki, T.; Matsunaga, S.; Hashimoto, K. *Tetrahedron Lett.* **1987**, *28*, 4313.
(9) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512.
(10) Garcia, J.; Lopez, M.; Romeu, J. *Synlett* **1999**, *4*, 429.
(11) Gung, B. W.; Dickson, H.; Shockley, S. *Tetrahedron Lett.* **2001**, *42*, 4761.
(12) Frantz, D. E.; Fassler, R.; Carreira, E. M. *J. Am. Chem. Soc.* **2000**, *122*, 1806.
(13) Trost, B. M.; Livingston, R. C. *J. Am. Chem. Soc.* **1995**, *117*, 9586. Cocatalysis with $In(OTf)_3$ and CSA improved rates and turnover: Livingston, R. C. Ph.D. Thesis, Stanford University, Stanford, CA, 1999.
(14) Zimmer, O. K.; Vollenberg, W. P.; Loschen, G. K. H.; Winter, W.; Kiesewetter, E. O.; Seippl, U. G. P. U.S. Patent 4959391, 1990. CAS 106853-30-9.
(15) These conditions were modified from a similar procedure described in ref 8.

Scheme 3. Total Synthesis of Adociacetylene B



catalyst loading (6 equiv of Me_2Zn/TMS acetylene, 20 mol % of **1**) cleanly led to dialkynylated product **9**. Deprotection with K_2CO_3 in methanol yielded pure adociacetylene B (**2**) with spectroscopic data in full agreement with published data.[5]

Three possible stereochemical products are possible: the two enantiomers of adociacetylene B and the undesired meso product. Because of the distal nature of the stereochemical information, the two diastereomers (meso and dl) were neither separable by column chromatography nor distinguishable by NMR spectroscopy. However, chiral HPLC analysis of the final product mixture proved sufficient to determine both the diastereomeric ratio and enantiomeric excess (Figure 2). When the final product mixture was

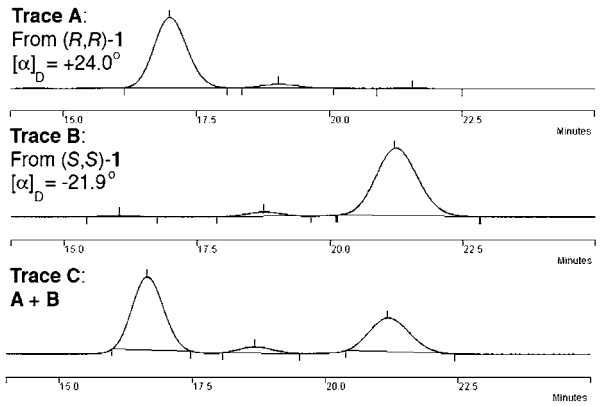


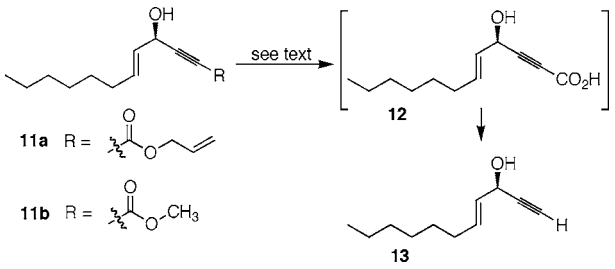
Figure 2. Chiral HPLC analysis of adociacetylene B.

subjected to chiral HPLC conditions, three distinct peaks were observed. The two enantiomeric peaks were assigned by comparison of the optical rotation of a given sample with known values. As predicted by our stereochemical model,[1] alkynylation with (*R*,*R*)-**1** yielded (+)-(*S*,*S*)-adociacetylene B ($[\alpha]_D = +24.0°$, $c = 0.9$, $CHCl_3$; lit.:[5] $[\alpha]_D = +21.7°$, $c = 0.38$, $CHCl_3$) (trace A), whereas (*S*,*S*)-**1** afforded (−)-(*R*,*R*)-adociacetylene B ($[\alpha]_D = -21.9°$, $c = 1.2$, $CHCl_3$) (trace B). The meso product was assigned as the minor peak between the two large enantiomeric peaks in the racemic sample (trace C).

With an accurate stereochemical assay, the product mixture from route A (Scheme 3) was determined to have a diastereomeric ratio of 9:1 (dl:meso) in remarkably high enantiomeric excess (>99% ee).

In an attempt to improve the diastereomeric ratio and encouraged by the excellent enantioselectivity we observed when methyl propiolate was used on linear, unbranched aldehydes (Scheme 2, **8c**), we chose to examine this nucleophile in the bisalkynylation. Subsequent decarboxylation would enable the use of propiolate as a protected ethyne, and methods for their decarboxylation were therefore examined (Scheme 4). Stimulated by the report of an

Scheme 4. Decarboxylation of Ynoic Esters



accidental decarboxylation of allyl propiolic esters[16] with catalytic $Pd(PPh_3)_4$, we envisioned a one-step Pd-catalyzed decarboxylation. To this end, the adduct of allyl propiolate and nonenal was used as a model system (Scheme 4). However, all attempts to decarboxylate the allyl propiolate **11a** with Pd^0 or Pd^{II} failed to give reasonable yields of the terminal alkyne **13** and instead yielded only deallylated product **12** and excessive decomposition. Although a Pd-

(16) Okamoto, S.; Ono, N.; Tani, K.; Yoshida, Y.; Sato, F. *J. Chem. Soc., Chem. Commun.* **1994**, 279.

catalyzed decarboxylation was not realized, the addition of 2.3 equiv of CuCl to a stirring solution of **12** in acetonitrile at ambient temperature for 6 h led to facile decarboxylation.[17] Thus, the allyl group was abandoned, and decarboxylation of methyl propiolate adduct **11b** was accomplished in a two-stage process: saponification with LiOH followed by treatment with CuCl.

With a method for decarboxylation in hand, we returned to the synthesis to test the viability of propiolate as a donor in the alkynylation of dialdehyde **4**. Subjection to the optimal conditions (6 equiv of Me_2Zn/propiolate, 20 mol % of **1**) yielded diol **10** (71%). Subsequent decarboxylation afforded adociacetylene B in high yield (70%) and better diastereomeric ratio 17:1 (dl:meso), while retaining the high enantiomeric excess (>99%) previously observed when TMS−acetylene was employed in the alkynylation.

Thus, a concise and highly diastereo- and enantioselective synthesis of both (+)- and (−)-adociacetylene B was developed through the use of our ruthenium-catalyzed redox isomerization of propargylic alcohols and dinuclear zinc-catalyzed asymmetric alkynylation. Furthermore, the facility of the copper-catalyzed decarboxylation of a propiolic acid allows methyl propiolate to serve as an efficient, inexpensive ethynyl anion equivalent.

Acknowledgment. We thank General Medical Sciences Institute of the National Institutes of Health (GM-33049) for their generous support of our programs. Mass spectra were provided by the Mass Spectrometry Facility, University of San Francisco, supported by the NIH Division of Research Resources.

Supporting Information Available: Experimental procedures and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0615836

(17) Caporusso, A. M.; Lardicci, L. *J. Chem. Soc., Perkin Trans. 1* **1983**, 949.