J|A|C|S
COMMUNICATIONS

Published on Web 07/18/2002

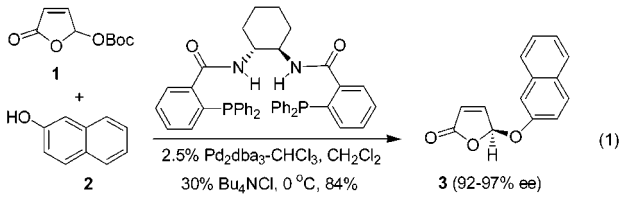
4-Aryloxybutenolides As "Chiral Aldehyde" Equivalents: An Efficient Enantioselective Synthesis of (+)-Brefeldin A

Barry M. Trost* and Matthew L. Crawley

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

Received April 5, 2002

Readily accessible "chiral aldehyde" equivalents play an important role in organic synthesis.[1] Enantiopure 4-aryloxybutenolides are readily available using a palladium-catalyzed asymmetric allylic alkylation (AAA) in a dynamic kinetic asymmetric transformation[2] as shown in eq 1. In the previous examples, the aryloxy group acted

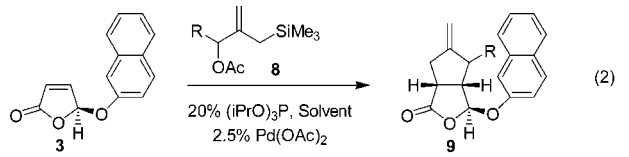


(1)

as a tether and was incorporated into the final product.[3] A significant aspect of the synthetic utility of γ-aryloxy or γ-alkoxybutenolides relies on the ability to transfer the chirality from the γ-alkoxy center to the α and β carbons in intermolecular reactions.[4] We became intrigued by this possibility in conjunction with our studies of enantioselectivity of cycloadditions of trimethylenemethane−palladium complexes (TMM−PdL_2) for asymmetric syntheses of cyclopentanoids. Asymmetric catalysis of this cycloaddition as well as using chiral auxiliaries on the acceptor has proven difficult.[5] In this work, we report the utility of the chiral acetal **3** for asymmetric cycloadditions, notably those involving TMM−PdL_2.

Previous reports have demonstrated the effectiveness of 5-menthyloxy-2-(5H)-furanone **5** in controlling diastereoselectivity of 1,3-dipolar and Diels−Alder cycloadditions.[6] For comparison, we examined an example of each as shown in Scheme 1. In both cases, as with **5**, facial selectivity of the cycloaddition as well as regioselectivity in the case of the 1,3-dipolar cycloaddition was complete to give adducts **6** and **7**. The yields were excellent, significantly higher in the case of **3** compared to **5** for the Diels−Alder reaction.[6] While we performed the Diels−Alder reaction in a normal thermal fashion (150 °C, 24 h, 68%), nearly quantitative yields were obtained using a microwave at 150 °C (60 min) or 165 °C (20 min).

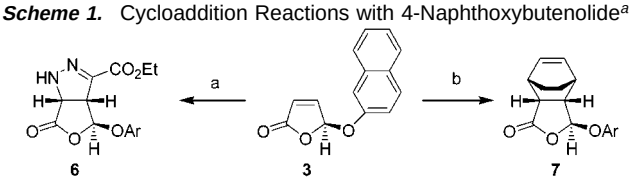
These results prompted us to examine the regio- and diastereoselectivity of cycloadditions via TMM−PdL_2[7] (eq 2). As sum-



(2)

marized in Table 1, a range of TMM precursors (**8a**−**8d**) were examined. All reacted well and gave complete control of regio-

Scheme 1. Cycloaddition Reactions with 4-Naphthoxybutenolide[a]



[a] (a) Ethyl diazoacetate, THF, Δ (94%). (b) 1,3-cyclohexadiene, microwave.

Table 1. TMM Cycloadditions to 4-Naphthoxybutenolide

entry	R =	conditions	yield	dr[a] (epi)[b]
a_1	H	Toluene, 100 °C, 12 h	93	>98/2
a_2		THF, 60 °C, 24 h	93	>98/2
b_1	CN[c]	THF, 60 °C, 12 h	94	5.5/1
b_2		Toluene, 100 °C, 6 h	91	94/6
c	Me	Toluene, 100 °C, 48 h	60	>98/2 (1/1)
d	Ph	Toluene, 100 °C, 24 h	79	>98/2 (4/1)

[a] All diastereomeric ratios are of the crude mixture. All diastereomers were separable by column chromatography. [b] Chiral center substituted with R group. [c] Olefin isomerized into conjugation with the nitrile.

selectivity and excellent facial selectivity. In the case of the cyano-substituted TMM reaction (entry b), the exocyclic double bond of the initial product isomerized to the endocyclic position. The solvent effect on the facial selectivity in this case is also noteworthy, that is, higher diastereoselectivity in toluene than THF even though the former is at considerably higher temperature. While the epimeric ratio with respect to the methyl group in entry c was 1:1, the ratio in the phenyl case increased to 4:1 (entry d).

The utility of the chiral aldehyde equivalent in the TMM−PdL_2 cycloaddition is demonstrated in the access it gives to a wide range of cyclopentane-containing natural products. Interest in the biological properties of (+)-brefeldin A **25**,[8] which continues to grow significantly,[9] provides a continuing stimulation for new synthetic strategies.[10] The chemistry reported herein provides a new opportunity to enhance the efficiency of a synthesis of this significant target.

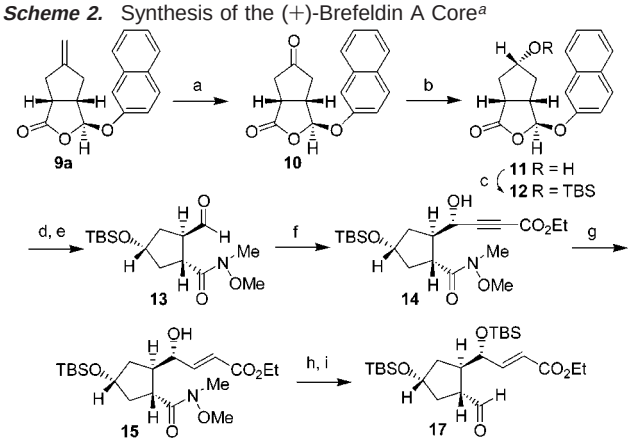
As shown in Scheme 2, the TMM cycloadduct **9a** was transformed to ketone **10** in 84% yield, utilizing a one-pot dihydroxylation−oxidative cleavage protocol.[11] Ketone **10** was chemo- and diastereoselectively (dr 96:4) reduced to alcohol **11** by the method of Yamamoto.[12] Without purification, the alcohol is silyl-protected to afford intermediate **12** in 74% yield (two steps.) Using a Merck protocol,[13] the lactone **12** is opened to the Weinreb amide/aldehyde, liberated 2-naphthol is removed (94% recovered), and the aldehyde is epimerized to afford the functionalized core **13** in 72% yield (two steps).

Introduction of the upper side chain envisioned use of a new protocol for formation of *trans*-alkenes from alkynes. Addition of the lithium anion of ethyl propiolate to the core **13** in 5/1 THF/

* To whom correspondence should be addressed. E-mail: bmtrost@stanford.edu.

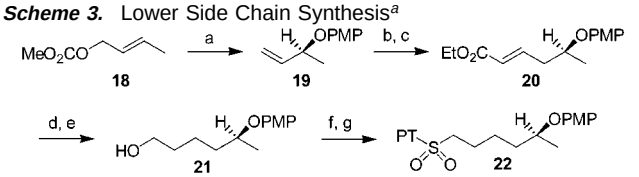
10.1021/ja026438b CCC: $22.00 © 2002 American Chemical Society

Scheme 2. Synthesis of the (+)-Brefeldin A Core[a]



[a] (a) $NaIO_4$, 5% OsO_4, THF/H_2O (84%). (b) DIBAL-H, B. H. T., Toluene (>96/4 dr).(c) TBDMSOTf, pyridine (74%, two Steps). (d) $(^iPr)_2MgCl$, MeO(Me)NH-HCl, THF, −10 °C. (e) DBU, CH_2Cl_2 (72%, two Steps). (f) $LiCCCO_2Et$, THF/HMPA = 5/1, −78 °C (>6:1 dr, 88%). (g) $(EtO)_3SiH$, 1% $Cp^*Ru(CH_3CN)_3PF_6$, CH_2Cl_2 (92%). (h) TBDMSOTf, pyridine, CH_2Cl_2. (i) DIBAL-H, THF, −78 °C (81%, two Steps).

Scheme 3. Lower Side Chain Synthesis[a]



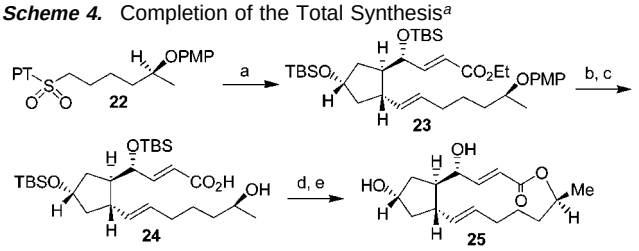
[a] *p*-Methoxyphenol, 0.25% Pd_2dba_3-$CHCl_3$, 0.75% ligand **4**, toluene (>96/4 regio., up to 90% ee, 95%). (b) 9-BBN, THF, then H_2O_2, aq NaOH. (c) PCC, CH_2Cl_2, Celite, 4Å MS then $EtO_2CC(H)PPh_3$ (65% two steps). (d) $NaBH_4$, MeOH, 5% $NiCl_2$, 0 °C. (e) DIBAL-H, THF (92%, two steps). (f) DIAD, PPh_3, 1-phenyl-5-thioltetrazole, THF. (g) Oxone, MeOH, H_2O, 60 °C (88%, two steps).

HMPA at −78 °C afforded propargyl alcohol **14** in 6:1 dr (88% yield) with Felkin−Ahn control, whereas the epimer was also available in 1:6 dr (92% yield) by simply using DME, presumably under chelation control. Exposing this adduct **14** to ruthenium-catalyzed *trans*-hydrosilylation[14] followed by addition of cesium fluoride and ethanol gave enoate **15** directly in one step in 92% yield. Thus, the upper side chain was introduced in two steps, and this sequence constitutes a convenient and general entry to γ-hydroxy-α,β-*trans*-enoates. After silyl protection, the amide **16** was chemoselectively reduced to aldehyde **17** in 81% yield in the presence of the enoate by utilizing one equivalent of DIBAL-H.

Scheme 3 summarizes the synthesis of the lower side chain. An enantio- and regioselective palladium-catalyzed AAA of crotyl carbonate **18** afforded the C(4) fragment **19** with 96:4 regioselectivity and 90% ee in 93% yield.[15] Olefin **19** was transformed to enoate **20** via hydroboration−oxidation followed by one-pot oxidation to the aldehyde and in situ Wittig reaction with an overall yield of 65%. Nickel dichloride-catalyzed sodium borohydride 1,4-reduction followed by DIBAL-H reduction converted the enoate **20** directly to saturated alcohol **21** in 92% yield (two steps). Completion of the sulfone component **22** involved Mitsonobu coupling of 1-phenyl-5-thioltetrazole followed by Oxone oxidation[16] in 88% yield.

Julia olefination proved nontrivial. Optimization involved use of KHMDS in DME at −78 °C, whereby a 12:1 *E*:*Z* selectivity for formation of alkene **23** was obtained (see Scheme 4). Completion of the synthesis proceeded uneventfully and employed the Yamaguchi method for macrolactonization.[17]

Scheme 4. Completion of the Total Synthesis[a]



[a] (a) KHMDS, DME, then **17** to rt (*E*/*Z* > 12/1, 81%). (b) C.A.N., 4:1 = acetone: water. (c) 1 N aq NaOH, THF, MeOH (76%, two steps). (d) MsCl, Et_3N, 2,4,6-trichlorobenzoyl chloride, xs. 4-DMAP, toluene, Δ (61%). (e) TBAF, THF, rt (77%).

The spectral data as well as the sign and magnitude of rotation matched those of an authentic sample of (+)-brefeldin A. Thus, (+)-brefeldin A is available in a convergent fashion from three components: aldehyde-amide **13**, ethyl propiolate, and sulfone **22**. All of the stereochemistry evolves from two palladium-catalyzed AAA reactions. The effectiveness of the introduction of the upper side chain via the new methodology described which achieves a clean chemoselective reduction of an alkyne to a *trans*-alkene is noteworthy. This work demonstrates the utility of **3**, which is available via a catalytic asymmetric route, as a "chiral aldehyde" equivalent, especially in TMM−PdL_2 cycloadditions.

Acknowledgment. We thank the National Science Foundation and the General Medical Sciences Institute of the National Institutes of Health (GM 13598) for their generous support of our work. Mass spectra were provided by the Mass Spectrometry Regional Center of the University of California-San Francisco, supported by the NIH Division of Research Resources.

Supporting Information Available: Experimental procedures for **7**, **9a**−**9d**, **14**, **15**, **19**, and **25** and characterization data for all compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) Trost, B. M.; Crawley, M. L. *J. Am. Chem. Soc.* **2000**, *122*, 6120 and references therein.
(2) For a review on dynamic kinetic transformations, see: Ward, R. S. *Tetrahedron: Asymmetry* **1995**, *6*, 1475.
(3) Trost, B. M.; Toste, F. D. *J. Am. Chem. Soc.* **1999**, *121*, 3543.
(4) Krief, A.; Lecomte, P.; Demounte, J. P.; Dumont, W. *Synthesis* **1990**, *275*.
(5) Trost, B. M.; Yang, B.; Miller, M. L. *J. Am. Chem. Soc.* **1989**, *111*, 6842.
(6) (a) Feringa, B. L.; de Jong, J. C.; van Bolhuis, F. *Tetrahedron: Asymmetry* **1991**, *2*, 1247. (b) Feringa, B. L.; Rispens, M. T.; Keller, E.; de Lange, B.; Zijlstra, R. W. J. *Tetrahedron: Asymmetry* **1994**, *5*, 607.
(7) Trost, B. M.; Chan, D. M. T. *J. Am. Chem. Soc.* **1983**, *105*, 2326.
(8) Singleton, V. L.; Bohonos, N.; Ullstrupp, J. *Nature* **1958**, *181*, 1072.
(9) Cushman, M.; Fox, B. M.; Vroman, J. A.; Fanwick, P. E. *J. Med. Chem.* **2001**, *44*, 3915 and references cited therein.
(10) For most recent syntheses: (a) Kim, D.; Lee, J.; Shim, P. J.; Lim, J. I.; Doi, T.; Kim, S. *J. Org. Chem.* **2002**, *67*, 772. (b) Ibid., 764. (c) Suh, Y.-G.; Seo, S. Y.; Jung, J.-K.; Park, O.-H.; Jeon, R. A. *Tetrahedron Lett.* **2001**, *42*, 691. (d) previous Trost-group synthesis: Trost, B. M.; Lynch, J.; Renaut, P.; Steinman, D. H. *J. Am. Chem. Soc.* **1986**, *108*, 284.
(11) Pappo, R.; Allen, D. S., Jr.; Lemieux, R. U.; Johnson, W. S. *J. Org. Chem.* **1956**, *21*, 478.
(12) Yamamoto, H.; Iguchi, S.; Nakai, H.; Hayashi, M. *J. Org. Chem.* **1979**, *44*, 1363.
(13) Williams, J. M.; Jobson, R. B.; Yasuda, N.; Marchegini, G.; Dolling, U. H.; Grabowski, E. J. J. *Tetrahedron Lett.* **1995**, *36*, 5461
(14) Trost, B. M.; Ball, Z. T. *J. Am. Chem. Soc.* **2001**, *123*, 12726.
(15) Trost, B. M.; Toste, F. D. *J. Am. Chem. Soc.* **1999**, *121*, 4545.
(16) Trost, B. M.; Curran, D. P. *Tetrahedron Lett.* **1981**, *22*, 1287.
(17) Yamaguchi, M.; Innaga, J.; Hirata, K. Saeki, H.; Katsuki, T. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989.

JA026438B