ORGANIC LETTERS

2002
Vol. 4, No. 9
1627−1630

Construction of the Benzylic Quaternary Carbon Center of Zoanthenol by Intramolecular Mizoroki–Heck Reaction of Enone

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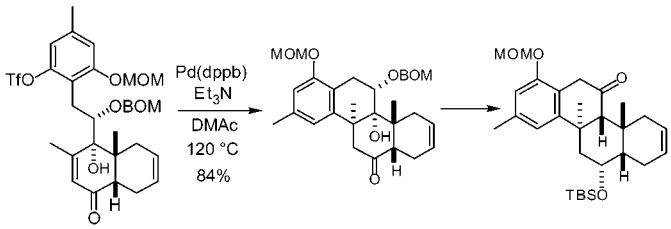
Received March 11, 2002

ABSTRACT



Stereocontrolled synthesis of the ABC ring framework of zoanthenol has been achieved. Our studies show that a β,β-disubstituted enone can act as a good acceptor of arylpalladium intermediates in the formation of a congested benzylic quaternary carbon center through an intramoleculer Mizoroki–Heck reaction. The *cis* B/C ring system was stereoselectively converted to the *trans*-fused framework through a SmI_2-promoted deoxygenation of the α-hydroxy ketone.

Zoanthamine alkaloids possess a densely functionalized heptacyclic structure and are unique in their topological complexity.[1] One of the critical obstacles in the total synthesis of zoanthamines[2,3] is the stereocontrolled construction of three consecutive quaternary carbon centers (C9, C12, and C22).[4] We have previously reported on our successful construction of the C12 center through an intramolecular Mizoroki−Heck reaction[5] using allylic ether **4**.[2c] However, despite our efforts, we were not able to improve the yield of the cyclization step above 43%; this was attributable to steric repulsions that were developing in the cyclization transition state.[2c] Herein, we describe an alternate and more efficient approach to the intramolecular Mizoroki−Heck reaction by utilizing enone **5** in place of the allylic ether **4** (Scheme 1). Furthermore, stereocontrolled synthesis of the *trans*-fused BC ring framework (**2**) of zoanthenol (**1**) was also achieved.

To facilitate the regioselective cyclization (Scheme 2; **A** → **B**), enone **5** was proposed as a sterically less demanding

(1) (a) Rao, C. B.; Anjaneyula, A. S. R.; Sarma, N. S.; Venkateswarlu, Y.; Rosser, R. M.; Faulkner, D. J.; Chen, M. H. M.; Clardy, J. *J. Am. Chem. Soc*. **1984**, *106*, 7983. (b) Kuramoto, M.; Hayashi, K.; Yamaguchi, K.; Yada, M.; Tsuji, T.; Uemura, D. *Bull. Chem. Soc. Jpn*. **1998**, *71*, 771. (c) Nakamura, H.; Kawase, Y.; Maruyama, K.; Murai, A. *Bull. Chem. Soc. Jpn*. **1998**, *71*, 781. (d) Deranas, A. H.; Fernández, J. J.; Gavín, J. A.; Norte, M. *Tetrahedron* **1999**, *55*, 5539.

(2) (a) Hirai, G.; Oguri, H.; Hirama, M. *Chem. Lett.* **1999**, 141. (b) Moharram, S. M.; Hirai, G.; Koyama, K.; Oguri, H.; Hirama, M. *Tetrahedron Lett.* **2000**, *41*, 6669. (c) Hirai, G.; Oguri, H.; Moharram, S. M.; Koyama, K.; Hirama, M. *Tetrahedron Lett.* **2001**, *42*, 5783.

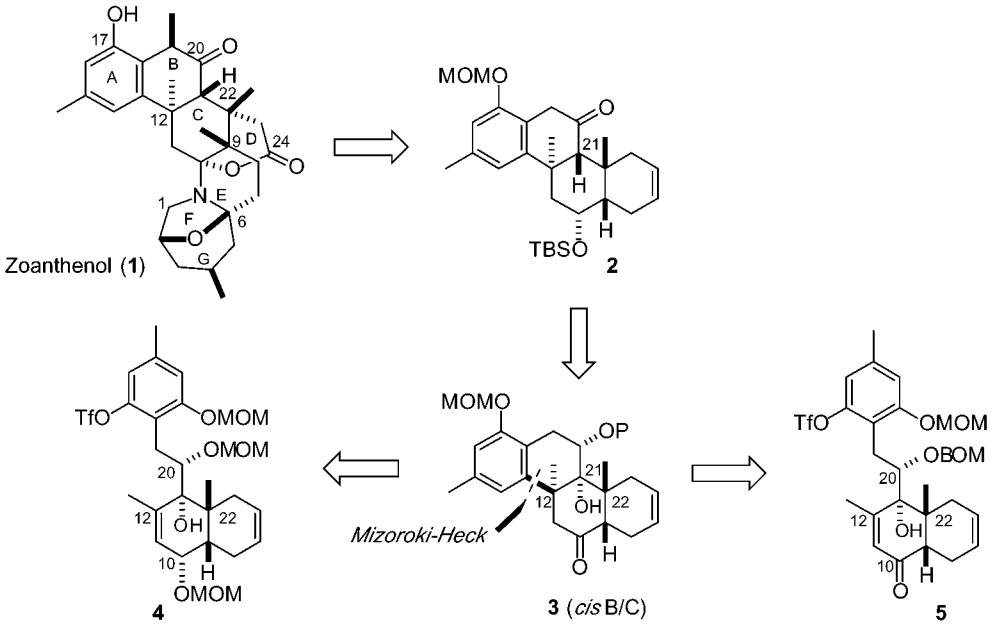
(3) For other synthetic studies, see: (a) Tanner, D.; Tedenborg, L.; Somfai, P. *Acta Chem. Scand*. **1997**, *51*, 1217. (b) Williams, D. R.; Cortez, G. S. *Org. Lett*. **2000**, *2*, 1023. (c) Hikage, N.; Furukawa, H.; Takao, K.; Kobayashi, S. *Chem. Pharm. Bull*. **2000**, *48*, 1370, and references therein.

(4) Carbon numbering corresponds to that for zoanthenol (**1**), see ref 1d.

(5) Excellent reviews, see: (a) Tsuji, J. *Palladium Reagent and Catalysts. Innovation in Organic Synthesis*; John Wiley: New York; 1995. (b) Link, J. T.; Overman, L. E. *Metal-catalyzed Cross Coupling Reaction*; Diederick, F. and Stang, P. J., Eds.; Wiley-VCH: Weinheim, 1998, Chapter 6. (c) Meijere, A. de.; Meyer, F. E. *Angew. Chem., Int. Ed. Engl*. **1994**, *33*, 2379. (d) Shibasaki, M.; Boden, C. D. J.; Kojima, A. *Tetrahedron* **199**7, *53*, 7371. (e) Beletskaya, I. P.; Cheprakov, A. V. *Chem. Rev*. **2000**, *100*, 3009.

10.1021/ol025852d CCC: $22.00
Published on Web 04/03/2002

Scheme 1. Synthesis Plan of **2**

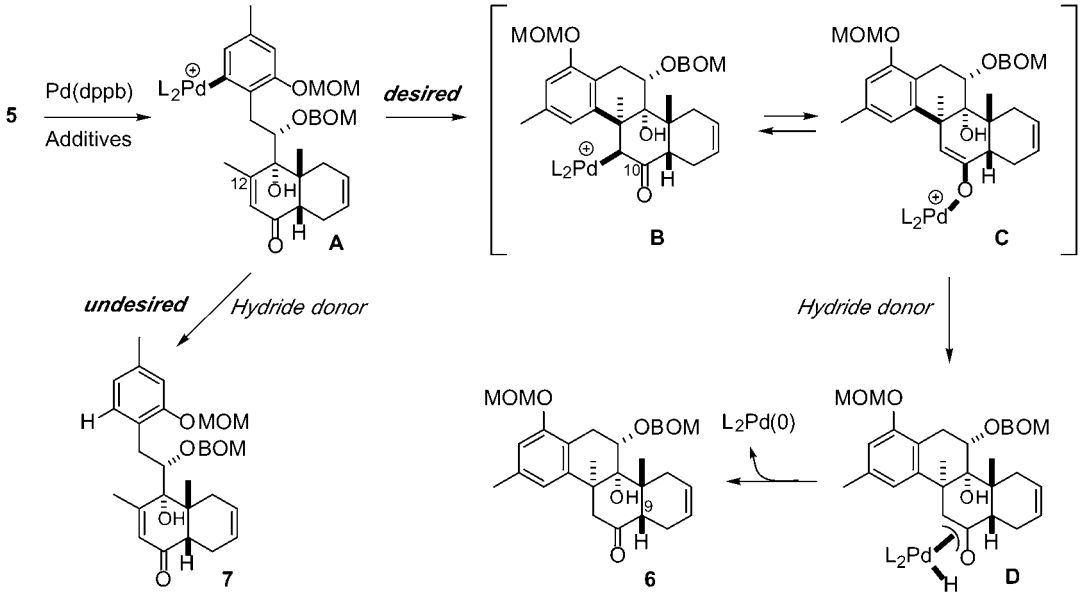


acceptor of the internal arylpalladium species.[6] Since intermediate **B** does not have a β-hydrogen, which is necessary for *syn*-elimination, a hydride donor was required in order to generate palladium hydride species **D**, which would lead to product **6** via reductive elimination.

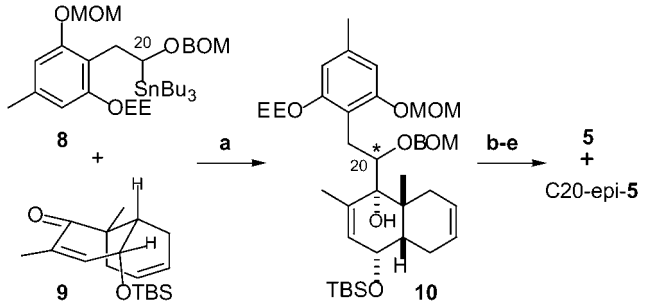
As shown in Scheme 3, synthesis of **5** was initiated with the coupling reaction between **8** and **9**, following reported protocols but with altered protecting groups.[2c] The silyl ether bond of the resulting inseparable C20-epimeric mixture of **10** was cleaved by TBAF in DMPU,[7] and then oxidized. Following the conversion of the ethoxyethyl ether (EE) into the triflate, the resulting epimers of **5** were separated using silica gel chromatography.

The palladium-catalyzed cyclization of **5**, in the presence of triethylamine or *N*,*N*-diisoproplyethylamine as possible hydride donors,[8] proceeded smoothly in a 6-exo fashion to afford tetracyclic **6** in good yield (>70%) (Table 1, entries 1 and 2). In contrast, cyclization in the presence of *n*-Bu_4NBr and HCO_2K[9] resulted in an exclusive formation of reduced **7** (entry 3). Addition of 1,2,2,6,6-pentamethylpiperidine (PMP)[10b] decreased the yield of **6**, and furthermore epimerization at C9 was observed (entry 4). Carrying out the

Scheme 2. A Plausible Mechanism for the Cyclization of **5**



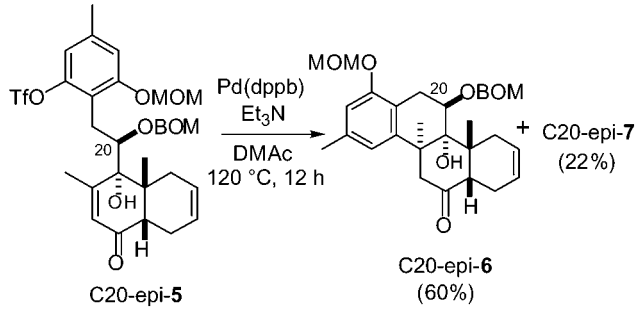
Scheme 3[a]



[a] (a) *n*-BuLi, **9** (1.3 equiv), THF, −78 °C; (b) TBAF, DMPU, 80 °C, 83% (two steps); (c) Dess−Martin periodinane, CH_2Cl_2; (d) PPTS, MeOH, 96% (two steps); (e) Tf_2O, Et_3N, CH_2Cl_2, −78 °C, **5** (57%), C20-epi-**5** (35%).

reaction under dilute conditions (0.05 M), in the presence of triethylamine, afforded **6** in a significantly higher yield (84%), possibly because of the suppressed intermolecular process that leads to undesired **7** (entry 5). Cyclization of C20-epi-**5**, under the dilute conditions, also afforded epi-**6** in 60% yield (Scheme 4). To the best of our knowledge,

Scheme 4



these reactions (**5** → **6**, epi-**5** → epi-**6**) are the first examples of the intramolecular Mizoroki−Heck reaction using β,β-disubstituted enones toward the construction of a benzylic quaternary center, as well as the first in an enone−triflate combination.[10,11]

(6) (a) For steric effects on the insertion of cationic palladium complex to olefins, see: Kawataka, F.; Shimizu, I.; Yamamoto, A. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 654. (b) For electronic effects, see: Cabri, W.: Candiani, I. *Acc. Chem. Res.* **1995**, *28*, 2, and references therein.

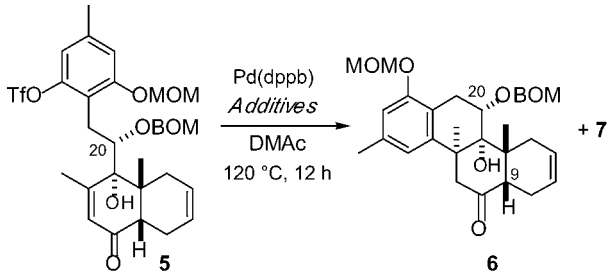
(7) TBS ether was not removed by TBAF in refluxing THF.

(8) (a) Murahashi, S.; Watanabe, T. *J. Am. Chem. Soc.* **1979**, *101*, 7429. (b) McCrindle, R.; Ferguson, G.; Arsenault, G. J.; McAlees, A. J. *J. Chem. Soc., Chem. Commun.* **1983**, 571. (c) Stokker, G. E. *Tetrahedron Lett.* **1987**, *28*, 3179.

(9) Larock, R. C.; Johnson, P. L. *J. Chem. Soc., Chem. Commun.* **1989**, 1368.

(10) For selected reports for cyclizations constructing a benzylic quaternary center, see: (a) Takemoto, T.; Sodeoka, M.; Sasai, H.; Shibasaki, M. *J. Am. Chem. Soc.* **1993**, *115*, 8477. (b) Overman, L. E. *Pure Appl. Chem.* **1994**, *66*, 1423. (c) Laschat, S.; Narjes, F.; Overman, L. E. *Teterahedron* **1994**, *50*, 347. (d) Rigby, J. H.; Deur, C.; Heeg, M. J. *Tetrahedron Lett.* **1999**, *40*, 6887. (e) Dras, E.; Guillou, C,; Thal, C. *Tetrahedron Lett.* **1999**, *40*, 9243. (f) Fukuyama, Y.; Matsumoto, K.; Tonoi, Y.; Yokoyama, R.; Takahashi, H.; Minami, H.; Okazaki, H.; Mitsumoto, Y. *Teterahedron* **2001**, *57*, 7127.

Table 1. Palladium-Catalyzed Cyclization of **5**[a]

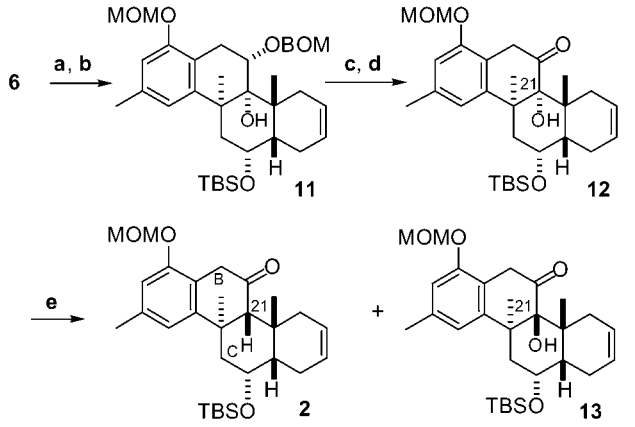


		yield of products (%)	
entry	additives (equiv)	**6**	**7**
1	Et_3N (10)	76	14
2	$(i\text{-}Pr)_2NEt$ (10)	74	19
3	$n\text{-}Bu_4NBr-HCO_2K$ (10)	0	71
4	Et_3N (5), PMP (5)	29[c]	4
5[b]	Et_3N (10)	84	5

[a] Conditions: $Pd_2(dba)_3{\cdot}CHCl_3$ (15 mol %), dppb (40 mol %) in DMAc (0.1 M) at 120 °C for 12 h in a sealed tube. [b] Diluted to 0.05 M. [c] A mixture of **6**:C9-epi-**6** = 1:1.

The subsequent steps describe the conversion of **6** into the *trans*-fused BC-ring of **2** (Scheme 5). Ketone **6** was

Scheme 5[a]



[a] (a) L-Selectride, THF, −78 °C; (b) TBSOTf, 2,6-lutidine, CH_2Cl_2, 92% (two steps); (c) Na, NH_3, THF, EtOH, −78 °C, 86%; (d) $(CF_3CO)_2O$, DMSO, Et_3N, CH_2Cl_2, −78 °C, 94%; (e) SmI_2, THF, rt, then H_2O, **2** (75%), **13** (17%).

reduced stereoselectively using L-Selectride and then transformed to silyl ether **11**. Following the removal of the benzyloxy methyl (BOM) group, the resulting alcohol was

(11) For cyclizations of α,β-unsaturated carbonyl compounds with aryl halides, see: (a) Friestad, G. K.; Branchaud, B. P. *Tetrahedron Lett.* **1995**, *36*, 7047. (b) Dankwardt, J. W.; Flippin, L. A. *J. Org. Chem.* **1995**, *60*, 2312. (c) Comins, D. L.; Joseph, S. P.; Zhang, Y. *Tetrahedron Lett.* **1996**, *37*, 793. (d) Yoneda, R.; Kimura, T.; Kinomoto, J.; Harusawa, S.; Kurihara, T. *J. Heterocycl. Chem.* **1996**, *33*, 1909. (e) Krischbaum, S.; Waldmann *J. Org. Chem.* **1998**, *63*, 4936. (f) Ikeda, M.; El Bialy, S. A. A.; Yakura, T. *Heterocycles* **1999**, *51*, 1957. (g) Imbos, R.; Minnaaed, A. J.; Feringa, B. L. *J. Am. Chem. Soc.* **2002**, *124*, 184.

oxidized with DMSO−$(CF_3CO)_2O$ to give α-hydroxy ketone **12**. Treatment of **12** with excess SmI_2 and subsequent protonation of the resulting enolate afforded **2** stereoselectively. Additionally, hydroxy ketone **13**, a C21 epimer of **12**, was also obtained as a minor product.[12]

In conclusion, we have developed an intramolecular Mizoroki−Heck reaction of *β*,*β*-disubstituted enones toward the formation of the congested benzylic quaternary center of **1**. This powerful methodology can be utilized in the syntheses of polycyclic skeletons of architecturally complex natural products. Further studies toward the total synthesis of **1** are currently in progress in our laboratory.

(12) While the mechanisms of the epimerization of **12** to **13** is yet unclear, Sm(III) species, which were formed in the reduction of **12**, might play a key role.

Acknowledgment. Fellowships to G.H. and S.M.M. from the Japanese Society for the Promotion of Science are gratefully acknowledged. We thank M. J. Lear for valuable discussions. This study was supported in part by the Suntory Institute for Bioorganic Research.

Supporting Information Available: Spectroscopic data for compounds **2**, **5**, epi-**5**, **6**, epi-**6**, **12**, and **13**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL025852D