

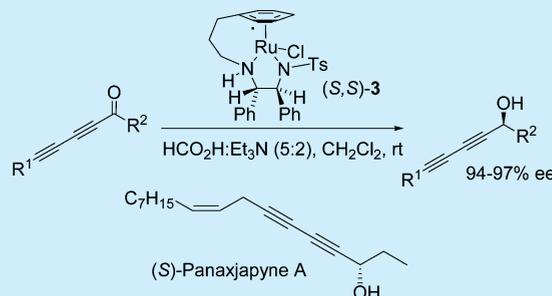
Asymmetric Reduction of Diynones and the Total Synthesis of (S)-Panaxjapyne A

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S Supporting Information

ABSTRACT: The asymmetric transfer hydrogenation of a series of diynones has been achieved in high conversion and enantiomeric induction. When R¹ is a phenyl group, a competing alkyne reduction takes place; however, when R¹ is an alkyl group, this side-reaction is not observed. The application of the reduction to the total synthesis of the natural product (S)-panaxjapyne A in high enantiomeric excess is described.



Diyneols are found in a number of natural products, some of which exhibit potent anticancer and anti-HIV properties.¹ Notable examples are strongylodiols A–C, isolated from the sponge genus *Strongylophora*, which possesses cytotoxic activities against tumor cells (DLD-1 and MOLT-4).² Diynol-containing natural products panaxjapyne A–C (Figure 1) were

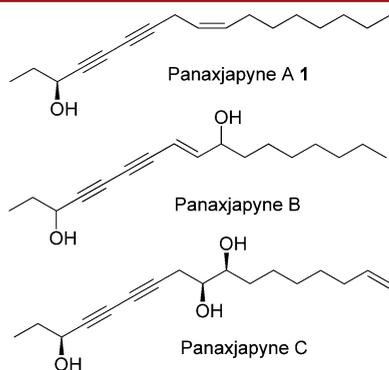


Figure 1. Structures of panaxjapyne A–C.

isolated as secondary metabolites from the roots of *Panax japonicus* C. A. Meyer var. major. Potent yeast α -glucosidase activity inhibitory effects have been reported for these three compounds, although to date a total synthesis of only panaxjapyne C has been reported; L-ascorbic acid was used as the source of chirality in this synthesis.³

Reported approaches to the asymmetric synthesis of diynols have predominantly involved the addition of 1,3-diyne to aldehydes. The first example was reported by Carreira et al., who employed a Zn(OTf)₂/N-methylephedrine ligand for the total syntheses of (R)-strongylodiols A and B⁴ in 82 and 80% ee, respectively. A modified protocol was reported by Tykwinski et al.⁵ Trost et al. published a systematic study of catalytic 1,3-diyne asymmetric additions to aldehydes using an

(S,S)-ProPhenol ligand.⁶ An amino-alcohol ligand system established by Wang et al. was also applied to the total synthesis of strongylodiols.⁷ Trost et al. found that low yields in additions to low molecular weight aldehydes were caused by a competing aldol reaction, but were able to obtain a product of 94% ee in up to 78% yield through slow addition of excess aldehyde.⁸ A recently reported 1,1'-binaphth-2-ol (BINOL)/ZnEt₂/Ti(OiPr)₄ system gave excellent results in this transformation, across a wide range of substrates.⁹

Although the addition of diynes to aldehydes is an effective method for the synthesis of diynols in high ee, it is often necessary to employ an excess of either a diyne or aldehyde. It therefore seemed desirable to develop an alternative approach to these valuable targets. The asymmetric transfer hydrogenation (ATH)¹⁰ of ketones adjacent to an alkyne is known to proceed in high enantioselectivity and yield when Ru(II) complexes **2** and **3** (Figure 2) are employed as catalysts.¹¹ To our knowledge, however, no report has yet been published on the synthesis of enantiomerically enriched diynols via the asymmetric reduction of diynones.

The synthesis of diynones required the use of the well established and efficient Cadiot–Chodkiewicz cross-coupling.¹² In this reaction, racemic 1-yne-3-ols, which are either

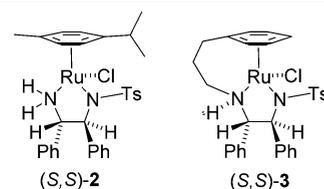
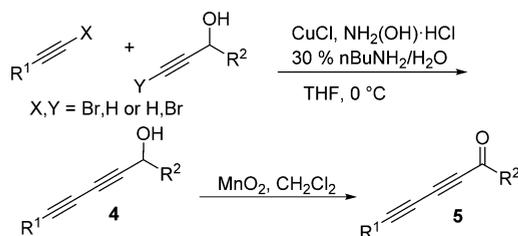


Figure 2. Tethered asymmetric reduction catalysts.

Received: November 7, 2013

commercially available or easily accessible, were used as coupling reagents. Eight racemic diynols **4a–h** were prepared¹² (Table 1) in good to excellent yields (72–98%). After purification, the resulting diynols were oxidized by activated MnO₂ powder, which is commonly used to oxidize ynols to ynone.¹³

Table 1. Synthesis of Diynones



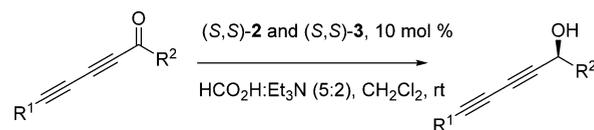
| entry | R ¹ | R ² | step 1 yield ^a % | step 2 yield ^a % |
|-------|---|---|-----------------------------|------------------------------|
| 1 | C ₆ H ₅ | CH ₃ | 90 (4a) | 98 (5a) |
| 2 | BnO(CH ₃) ₂ C | CH ₃ | 79 (4b) | 85 (5b) |
| 3 | <i>n</i> -C ₄ H ₉ | CH ₃ | 69 (4c) | – (5c) ^b |
| 4 | <i>n</i> -C ₄ H ₉ | <i>n</i> -C ₃ H ₇ | 88 (4d) | 82 (5d) |
| 5 | HO(CH ₂) ₄ | CH ₃ | 98 (4e) | 90 (5e) |
| 6 | <i>n</i> -C ₄ H ₉ | CH ₂ C ₆ H ₅ | 72 (4f) | 25 (5f) |
| 7 | BnO(CH ₂) ₃ C | CH ₃ | 97 (4g) | 71 (5g) |
| 8 | BnO(CH ₃) ₂ C | <i>i</i> -C ₃ H ₇ | 73 (4h) | 98 (5h) |

^aIsolated yield. ^bThis compound was not isolated.

With the exception of entry 6, clean diynones **5a–h** were formed as the only products, and these were easily isolated using silica gel column chromatography. Activated MnO₂ powder oxidizes diynols preferentially without breaking the electron-rich 1,3-diyne bond or oxidizing a terminal hydroxyl group (entry 5). In entry 6 the resulting ketone is more likely to enolize, which may explain why the yield is lower than the others. In entry 3 pure diynone was not separated because of its high volatility and was used as a CH₂Cl₂ solution in the next step.

Initially, 6-phenyl-3,5-hexadiyn-2-one **5a** was selected for testing in the ATH reaction.^{10,11} It was found that the ATH of this compound was problematic. The ketone was prone to decomposition in both TEA and HCO₂Na, and during the reduction reaction, a side reaction was detected (Table 2, entry 1). Peaks were observed in the ¹H NMR spectrum of the product at 5.72 and 6.64 ppm (see Supporting Information). TLC analysis showed a spot close to that of 6-phenyl-3,5-hexadiyn-ol. This suggested that a competing hydrogen transfer process takes place on the dialkyne to give a number of alkyne reduction products. Although the isolated yield of **4a** was low (25%), its ee was 94%. It was thought that a bulky group at the end of the diyne might slow down the rate of alkyne reduction. In the event, the ketone bearing a BnO(CH₃)₂C group (entry 2) exhibited greater stability in HCO₂H/TEA 5:2 CH₂Cl₂ solution. Furthermore, during the ATH reduction, only a trace amount (<5%) of the alkyne reduction product was detected in the ¹H NMR spectrum. The relatively low reactivities of diynones **5** required the catalyst loading to be increased to 10 mol % to allow the reaction to finish within a short reaction time (3 h when (*S,S*)-**2** was used, 1 h when (*S,S*)-**3** was used). At lower loadings, longer times were required, and some decomposition was observed. The reduction of diynones containing an aliphatic chain gave products in both excellent

Table 2. ATH of Diynones



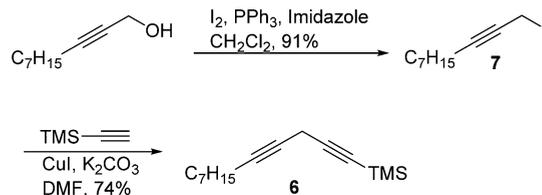
| entry | R ¹ | R ² | yield ^{a,b} % | ee ^{a,b,c} % |
|-------|---|---|------------------------|-----------------------|
| 1 | C ₆ H ₅ | CH ₃ (4a) | 25 | 94 |
| 2 | BnO(CH ₃) ₂ C | CH ₃ (4b) | 86 (82) | 94 (93) |
| 3 | <i>n</i> -C ₄ H ₉ | CH ₃ (4c) | 94 (75) | 97 (97) |
| 4 | <i>n</i> -C ₄ H ₉ | <i>n</i> -C ₃ H ₇ (4d) | 91 (95) | 97 (98) |
| 5 | HO(CH ₂) ₄ | CH ₃ (4e) | 89 (96) | >90 (>90) |
| 6 | <i>n</i> -C ₄ H ₉ | CH ₂ C ₆ H ₅ (4f) | 90 (92) | 97 (98) |
| 7 | BnO(CH ₂) ₃ C | CH ₃ (4g) | 85 (76) | 95 (90) |
| 8 | BnO(CH ₃) ₂ C | <i>i</i> -C ₃ H ₇ (4h) | 79 (95) | 96 (99) |

^aIsolated yield and ee using catalyst (*S,S*)-**2**. Reaction time 3 h. ^bee values were determined by chiral HPLC. ^cFigures in brackets are yields and ees achieved by using catalyst (*S,S*)-**3**. Reaction time 1 h.

yield (up to 95%) and ee (up to 99%). In the example shown in entry 5, even with a free hydroxyl group on the side of the R¹ group, neither the conversion nor the selectivity of the reduction was compromised. In one case (**4c**), the sign of the optical rotation matched that previously reported,¹⁴ serving to confirm the (*S*) configuration that was anticipated on the basis of the reduction of ynones.¹¹ The configurations of the other products were assigned by analogy.

A route to panaxajapyne **1**^{3a} was developed, via 1,4-diyne intermediate **6**¹⁵ (Scheme 1). 1-Iodo-2-decyne **7** was prepared

Scheme 1. Synthesis of Skipped Diyne 6



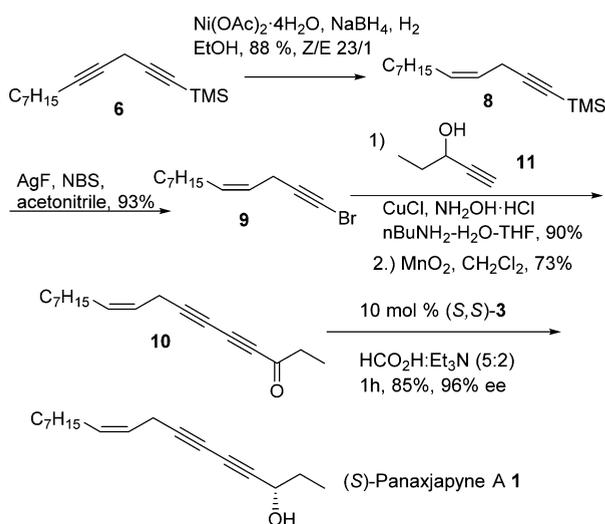
in high yield using the combination of I₂, PPh₃, and imidazole. The resulting product was combined with ethynyltrimethylsilane using the procedure reported by Prati et al.¹⁶ It was found that the product was formed as a single regioisomer by ¹H NMR and in good yield. The skipped diyne **6**, however, is unstable and therefore needs to be used freshly or stored in hexane at low temperature.

A regio- and *Z*-selective hydrogenation using a P-2 Ni catalyst was adopted to prepare (*4Z*)-4-dodecen-1-ynyltrimethylsilane **8**.¹⁷ To achieve a good yield and *Z/E* selectivity, it was found that the in situ generated P-2 Ni has to be poisoned by ethylenediamine for at least 1.5 h and the reaction must be complete in 1 h. The yield decreased (33%) when the reaction time was extended to 3.5 h, probably because of the base sensitivity of the TMS acetylene. The highest *Z/E* selectivity measured by ¹H NMR was *Z/E* = 23/1. Decreasing the poisoning time caused a drop in the *Z/E* selectivity. Subsequent AgF and NBS-mediated desilylbromination gave the corresponding bromoalkyne **9** in excellent yield.¹⁸

A Cadiot–Chodkiewicz cross-coupling¹² was used to link bromoalkyne **9** and 1-pentyn-3-ol **11** together. Under the conditions modified by Marino and Nguyen,^{12b} the coupling was completed within 30 min. The MnO₂ oxidation was clean,

and only product **10** could be detected by TLC. From the ATH reaction of **10**, enantiomerically enriched (*S*)-panaxjapyne **1** was isolated in 85% yield and 96% ee (Scheme 2), as determined by analysis of racemic panaxjapyne **1** and chiral HPLC of the panaxjapyne **1** 4-methoxybenzoate.

Scheme 2. Completion of the Synthesis of (*S*)-Panaxjapyne **1**



The experimental data for synthetic panaxjapyne **1**, including ^1H NMR, ^{13}C NMR, optical rotation and Mosher ester, were consistent with that reported for the natural material (see Supporting Information). The absolute configuration of **1** was assigned as (*S*) by comparing the ^1H NMR spectra of the Mosher ester derivatives of our racemic and enantiomerically enriched panaxjapyne **1** samples (see Supporting Information).¹⁹

In summary, we have demonstrated, for the first time, that diynones are suitable substrates for asymmetric transfer hydrogenation in high ee and conversion. The value of this methodology has been demonstrated in its application to the total synthesis of panaxjapyne **1**.

■ ASSOCIATED CONTENT

● Supporting Information

Full experimental details and analytical data including NMR spectra and chiral HPLC analyses. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank Warwick University for partial support of Y.F. and Johnson Matthey (Cambridge) for a generous gift of catalyst **3**.

■ REFERENCES

- (1) (a) Gung, B. W. *C. R. Chim.* **2009**, *12*, 489–505. (b) Yamaguchi, M.; Park, H.; Hiram, M. *Chem. Lett.* **1997**, 535–536. (c) Horikawa, K.; Yagyu, T.; Yoshioka, Y.; Fujiwara, T.; Kanamoto, A.; Okamoto, T.; Ojika, M. *Tetrahedron* **2013**, *69*, 101–106.
- (2) (a) Watanabe, K.; Tsuda, Y.; Yamane, Y.; Takahashi, H.; Iguchi, K.; Naoki, H.; Fujita, T.; Van Soest, R. W. M. *Tetrahedron Lett.* **2000**, *41*, 9271–9276. (b) Kirkham, J. E. D.; Courtney, T. D. L.; Lee, V.; Baldwin, J. E. *Tetrahedron* **2005**, *61*, 7219–7932.
- (3) (a) Chan, H. H.; Sun, H. D.; Reddy, M. V. B.; Wu, T. S. *Phytochemistry* **2010**, *7*, 1360–1364. (b) Thakur, P.; Kumaraswamy, B.; Reddy, G. R.; Bandichhor, R.; K. Mukkanti, K. *Tetrahedron Lett.* **2012**, *53*, 3703–3705.
- (4) Reber, S.; Knöpfel, T. F.; Carreira, E. M. *Tetrahedron* **2003**, *59*, 6813–6817.
- (5) Graham, E. R.; Tykwinski, R. R. *J. Org. Chem.* **2011**, *76*, 6574–6583.
- (6) Trost, B. M.; Chan, V. S.; Yamamoto, D. *J. Am. Chem. Soc.* **2010**, *132*, 5186–5192.
- (7) Zheng, B.; Li, S.-N.; Mao, J.-Y.; Wang, B.; Bian, Q.-H.; Liu, S.-Z.; Zhong, J.-C.; Guo, H.-C.; Wang, M. *Chem.—Eur. J.* **2012**, *18*, 9208–9211.
- (8) Trost, B. M.; Quintard, A. *Angew. Chem., Int. Ed.* **2012**, *51*, 6704–6708.
- (9) Turlington, M.; Du, Y.; Ostrum, S. G.; Santosh, V.; Wren, K.; Lin, T.; Sabat, M.; Pu, L. *J. Am. Chem. Soc.* **2011**, *133*, 11780–11794.
- (10) (a) Clapham, S. E.; Hadzovic, A.; Morris, R. H. *Coord. Chem. Rev.* **2004**, *248*, 2201–2237. (b) Gladiali, S.; Alberico, E. *Chem. Soc. Rev.* **2006**, *35*, 226–236. (c) Ikariya, T.; Murata, K.; Noyori, R. *Org. Biomol. Chem.* **2006**, *4*, 393–406. (d) Ikariya, T.; Blacker, A. J. *Acc. Chem. Res.* **2007**, *40*, 1300–1308. (e) Wang, C.; Wu, X.; Xiao, J. *Chem.—Asian J.* **2008**, *3*, 1750–1770. (f) Hashiguchi, S.; Fujii, A.; Takehara, J.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1995**, *117*, 7562–7563. (g) Fujii, A.; Hashiguchi, S.; Uematsu, N.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1996**, *118*, 2521–2522. (h) Haack, K. J.; Hashiguchi, S.; Fujii, A.; Ikariya, T.; Noyori, R. *Angew. Chem., Int. Ed.* **1997**, *36*, 285–288. (i) Handgraaf, J.-W.; Meijer, E. J. *J. Am. Chem. Soc.* **2007**, *129*, 3099–3103. (j) Soni, R.; Cheung, F. K.; Clarkson, G. C.; Martins, J. E. D.; Graham, M. A.; Wills, M. *Org. Biomol. Chem.* **2011**, *9*, 3290–3294. (k) Steward, K. M.; Gentry, E. C.; Johnson, J. S. *J. Am. Chem. Soc.* **2012**, *134*, 7329–7332. (l) Cheung, F. K.; Lin, C.; Minissi, F.; Lorente Crivillé, A.; Graham, M. A.; Fox, D. J.; Wills, M. *Org. Lett.* **2007**, *9*, 4659–4662. (m) Soni, R.; Collinson, J.-M.; Clarkson, G. C.; Wills, M. *Org. Lett.* **2011**, *13*, 4304–4307. (n) Hems, W. P.; Jackson, W. P.; Nightingale, P.; Bryant, R. *Org. Process Res. Dev.* **2012**, *16*, 461–463.
- (11) (a) Matsumura, K.; Hashiguchi, S.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1997**, *119*, 8738–8739. (b) Druais, V.; Meyer, C.; Cossy, J. *Org. Lett.* **2012**, *14*, 516–519. (c) Dias, L. C.; Ferreira, M. A. B. *J. Org. Chem.* **2012**, *77*, 4046–4062. (d) Gallon, J.; Esteban, J.; Bouzbouz, S.; Campbell, M.; Reymond, S.; Cossy, J. *Chem.—Eur. J.* **2012**, *18*, 11788–11797. (e) Mi, X.; Wang, Y.; Zhu, L.; Wang, R.; Hong, R. *Synthesis* **2012**, *44*, 3432–3440. (f) Arai, N.; Satoh, H.; Utsumi, N.; Murata, K.; Tsutsumi, K.; Ohkuma, T. *Org. Lett.* **2013**, *15*, 3030–3033. (g) Raghavan, S.; Vinoth Kumar, V. *Org. Biomol. Chem.* **2013**, *11*, 2847–2858. (h) Kesava Reddy, N.; Chandrasekhar, S. *J. Org. Chem.* **2013**, *78*, 3355–3360. (i) Trost, B. M.; Bartlett, M. J. *Org. Lett.* **2012**, *14*, 1322–1325.
- (12) (a) Chodkiewicz, W.; Cadiot, P. C. R. *Hebd. Seances Acad. Sci.* **1955**, *241*, 1055–1057. (b) J. P. Marino, J. P.; Nguyen, H. N. *J. Org. Chem.* **2002**, *67*, 6841–6844. (c) García-Domínguez, P.; Alvarez, R.; De Lera, A. R. *Eur. J. Org. Chem.* **2012**, 4762–4782. (d) Gung, B. W.; Gibeau, C.; Jones, A. *Tetrahedron: Asymmetry* **2004**, *15*, 3973–3977. (e) Sabitha, G.; Reddy, C. S.; Yadav, J. S. *Tetrahedron Lett.* **2006**, *47*, 4513–4516. (f) Gung, B. W.; Craft, D. T.; Truelove, J. *Tetrahedron: Asymmetry* **2007**, *18*, 1284–1287. (g) Domnin, I. N.; Remizova, L. A. *Russ. J. Org. Chem.* **2009**, *45*, 1123–1127. (h) Bonney, K. J.; Braddock, D. C. *J. Org. Chem.* **2012**, *77*, 9574–9584.
- (13) Aiguade, J.; Hao, J.; Forsyth, C. J. *Org. Lett.* **2001**, *3*, 979–982.
- (14) Birman, V. B.; Guo, L. *Org. Lett.* **2006**, *8*, 4859–4861.
- (15) Caruso, T.; Spinella, A. *Tetrahedron: Asymmetry* **2002**, *13*, 2071–2073.

- (16) Morandi, S.; Pellati, F.; Benvenuti, S.; Prati, S. F. *Tetrahedron* **2008**, *64*, 6324–6328.
- (17) Brown, C. A.; Ahuja, V. K. *J. Org. Chem.* **1973**, *38*, 2226–2230.
- (18) Lee, T.; Kang, H. R.; Kim, S.; Kim, S. *Tetrahedron* **2006**, *62*, 4081–4085.
- (19) (a) Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092–4096. (b) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512–519.