Asymmetric reduction of diynones and the total synthesis of (*S*)-panaxjapyne A

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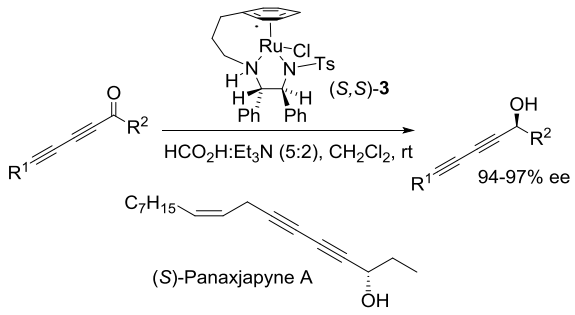
ABSTRACT



The asymmetric transfer hydrogenation of a series of diynones has been achieved in high conversion and enantiomeric induction. When R^1 is a phenyl group, a competing alkyne reduction takes place, however when R^1 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.

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

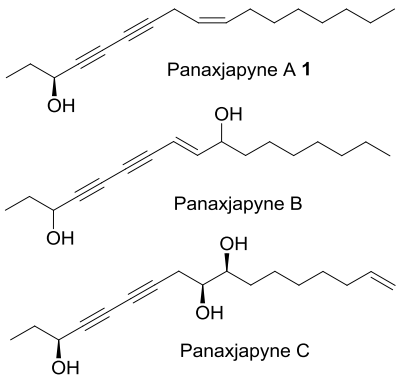


Figure 1. Structures of Panaxjapynes A-C.

Reported approaches to the asymmetric synthesis of diynols have predominantly involved the addition of 1,3-diynes 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 B[4] in 82% ee 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 el 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)/$ZnEt_2$/$Ti(OiPr)_4$ 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 be 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 eniched diynols via the asymmetric reduction of diynones.

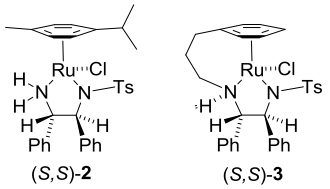
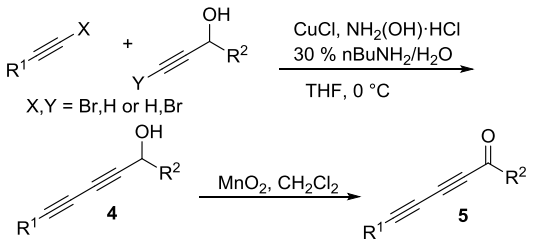


Figure 2. Tethered asymmetric reduction catalysts.

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 commercially available or easily accessible were used as coupling reagents. Eight racemic diynols **4a-h** were prepared[12] (Table 1) in good to excellent yields (72-98%). After purification, the resulting diynols were oxidized by activated MnO_2 powder, which is commonly used to oxidize ynols to ynones.[13]

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 MnO_2 power 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 due to its high volatility and was used as a CH_2Cl_2 solution in the next step.

Table 1. Synthesis of diynones.



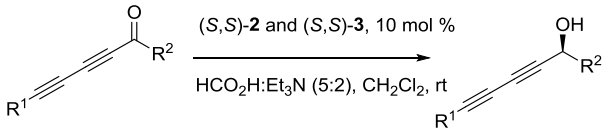
entry	R^1	R^2	step 1 yield[1] %	step 2 yield[1] %
1	C_6H_5	CH_3	90 (**4a**)	98 (**5a**)
2	$BnO(CH_3)_2C$	CH_3	79 (**4b**)	85 (**5b**)
3	*n*-C_4H_9	CH_3	69 (**4c**)	- (**5c**)[2]
4	*n*-C_4H_9	*n*-C_3H_7	88 (**4d**)	82 (**5d**)
5	$HO(CH_2)_4$	CH_3	98 (**4e**)	90 (**5e**)
6	*n*-C_4H_9	$CH_2C_6H_5$	72 (**4f**)	25 (**5f**)
7	$BnO(CH_2)_5C$	CH_3	97 (**4g**)	71 (**5g**)
8	$BnO(CH_3)_2C$	*i*-C_3H_7	73 (**4h**)	98 (**5h**)

1. Isolated yield. 2. This compound was not isolated.

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 HCO_2Na 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 $BnO(CH_3)_2C$ group (Entry 2) exhibited greater stability in HCO_2H/TEA 5:2 CH_2Cl_2 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 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 R^1 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 based on the reduction of ynones.[11] The configurations of the other products were assigned by analogy.

Table 2. ATH of diynones.

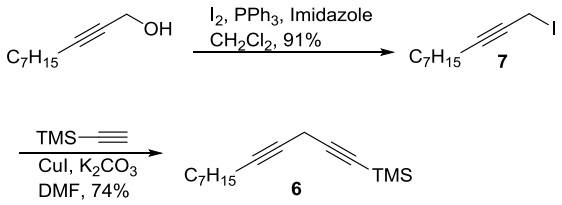


entry	R^1	R^2	yield[1,2] %	ee[1,2,3] %
1	C_6H_5	CH_3 (**4a**)	25	94
2	$BnO(CH_3)_2C$	CH_3 (**4b**)	86 (82)	94 (93)
3	*n*-C_4H_9	CH_3 (**4c**)	94 (75)	97 (97)
4	*n*-C_4H_9	*n*-C_3H_7 (**4d**)	91 (95)	97 (98)
5	$HO(CH_2)_4$	CH_3 (**4e**)	89 (96)	>90 (>90)
6	*n*-C_4H_9	$CH_2C_6H_5$ (**4f**)	90 (92)	97 (98)
7	$BnO(CH_2)_5C$	CH_3 (**4g**)	85 (76)	95 (90)
8	$BnO(CH_3)_2C$	*i*-C_3H_7 (**4h**)	79 (95)	96 (99)

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

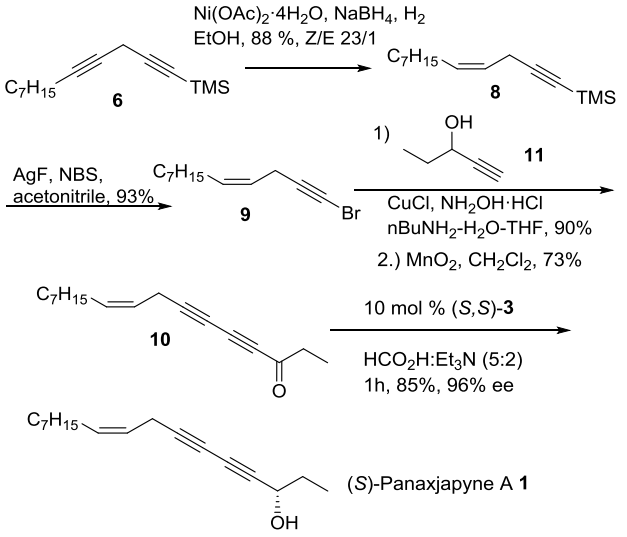
A route to panaxjapyne A **1**[3a] was developed, via 1,4-diyne intermediate **6**[15] (Scheme 1). 1-Iodo-2-decyne **7** was prepared in high yield using the combination of I_2, PPh_3 and imidazole. The resulting product was combined with ethynyltrimethylsilane using the procedure reported by Prati et al.[16] It was found that the product was formed as a single regioisomer by ^{1}H 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.

Scheme 1. Synthesis of skipped diyne **6**.



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 due to the base sensitivity of the TMS acetylene. The highest *Z*/*E* selectivity measured by ^{1}H 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]

Scheme 2. Completion of the synthesis of (*S*)-panaxjapyne A **1**.



A Cadiot-Chodkiewicz cross-coupling[12] 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 MnO_2 oxidation was clean, and only product **10** could be detected by TLC. From the ATH reaction of **10**, enantiomerically enriched (S)-panaxjapyne A **1** was isolated in 85% yield and 96% ee (Scheme 2), as determined by analysis of racemic panaxjapyne A and chiral HPLC of the panaxjapyne A 4-methoxybenzonate.

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

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Supporting Information Available: 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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