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# (+)-NYASOL FROM *ASPARAGUS COCHINCHINENSIS*

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**Key Word Index**—*Asparagus cochinchinensis*; Liliaceae; tuber; nyasol; hinokiresinol; norlignan.

**Abstract**—Bio-directed fractionation of the tubers of *Asparagus cochinchinensis* yielded the novel compound, (+)-nyasol. The structure and stereochemistry of (+)-nyasol was determined from two-dimensional NMR spectroscopy. It is proposed that the previously isolated natural product hinokiresinol is identical to nyasol.


## INTRODUCTION

*Asparagus cochinchinensis* is used in traditional medicine in Hong Kong for treating pulmonary tuberculosis, bronchitis and breast cancer [1]. A previous investigation of *A. cochinchinensis* has yielded a number of furostane glycosides [2].

## RESULTS AND DISCUSSION

Extraction of the tubers *A. cochinchinensis* with dichloromethane yielded an extract showing significant activity in the brine shrimp bio-assay (1000 $\mu$g ml$^{-1}$) [3]. Bio-assay directed fractionation (using the same bio-assay system) by CC yielded **1** as the only component of the extract to show significant activity (20 $\mu$g ml$^{-1}$).

Accurate mass spectrometry established the composition $C_{17}H_{16}O_2$ for **1** and IR showed the presence of a hydroxyl group(s) and unsaturation in the corresponding diagnostic regions. $^{13}$C NMR in $CDCl_3$ solution resolved only 13 resonances, four of which ($\delta$ 130.0, 128.9, 115.4 and 115.1) appeared to be of double intensity. $^1$H NMR confirmed the presence of eight aromatic protons, present as two AA'BB'-systems ($\delta$ 7.17 [2H], 7.10 [2H], 6.78 [2H], 6.77 [2H]). These two observations, taken together, suggested the presence of two *para*-disubstituted benzene groups in the structure of **1**. Two-dimensional correlation experiments (single-bond carbon–proton correlation, long-range carbon–proton correlation and proton–proton COSY) allowed these two aromatic groups to be assembled together with a 1,3-disubstituted 1,4-pentadiene system into the full structure of **1**; it also permitted unambiguous assignments for every $^{13}$C and $^1$H resonance (see Table 1).

Review of the literature revealed two reports of two natural products with the same gross structure as **1**. Hinokiresinol [4–6] was reported as having *trans*-stereochemistry at the 1,2-double bond on the basis of IR evidence, whilst nyasol [7–9] ($[\alpha]_D$ -147°, herein referred to as (–)-nyasol), was assigned the *cis*-isomer on the basis of coupling evidence in $^1$H NMR. Our data for **1** gave a reasonable match for both compounds (although reported data for hinokiresinol was somewhat limited). It was not possible to make a direct comparison between these two reported natural products from the physical and spectral data available, but we were surprised to note that both compounds apparently shared the same 12 Hz coupling constant for the protons of the 1,2-double-bond, which is unlikely if they are truly geometrical isomers. Indeed, in the case of *trans*-hinokiresinol it has been noted that the value of this coupling constant was "at the low end of the range" [10], whilst for *cis*-(–)-nyasol the authors observed that the coupling constant "is at the upper limit" [7]. An early synthesis of hinokiresinol [10] seems to confirm the *trans*-stereochemistry claimed for the natural product (both natural [4] and synthetic [10] products showed an IR absorbance at 967 cm$^{-1}$, interpreted as being due to a *trans* double bond), whilst a subsequent synthetic paper suggested that hinokiresinol was, in fact, the *cis*-isomer (synthesis of dimethyl ether analogues apparently showed $J_{1,2} = 11.3$ for *cis*-stereochemistry and $J_{1,2} = 15.9$ for *trans*) [11].

Since we had already established the complete assignments for every proton in the spectrum of **1**, it was a relatively simple matter to establish the geometry of the 1,2-double bond in the natural product from *A. cochinchinensis*, independently of the confusing IR and NMR arguments employed previously for the natural products and the contradictory results from synthesis, through the application of Nuclear Overhauser Enhancements. Correlations observed in NOESY spectra showed clearly that **1** had *cis*-stereochemistry (see Fig.

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Table 1. $^1H$ and $^{13}C$ NMR spectral data for compound **1** ($CDCl_3$)

| Assignment | $\delta^{13}C$ | Mult.* | $\delta^1H$ | 2 and 3 bond $^{13}C$ correlations to $^1H$ at: | $^1H$ correlations to $^1H$ at: |
|---|---|---|---|---|---|
| 1 | 128.6 | CH | 6.51 | | 5.67 |
| 2 | 131.7 | CH | 5.67 | | 6.51, 4.51 |
| 3 | 46.8 | CH | 4.51 | | 5.67, 6.00, 5.17, 5.15 |
| 4 | 140.7 | CH | 6.00 | | 5.17, 5.15, 4.51 |
| 5 | 115.0 | $CH_2$ | 5.15 | | 6.00, 4.51 |
| | | | 5.17 | | 6.00, 4.51 |
| 1′ | 129.8 | C | | 5.67, 6.78 | |
| 2′,6′ | 130.0 | CH | 7.17 | 6.51 | 6.78 |
| 3′,5′ | 115.1 | CH | 6.78 | | 7.17 |
| 4′ | 154.6 | C | | 7.17 | |
| 1″ | 135.5 | C | | 6.77 | |
| 2″,6″ | 128.9 | CH | 7.10 | | 6.77 |
| 3″,5″ | 115.4 | CH | 6.77 | | 7.10 |
| 4″ | 154.1 | C | | 7.10 | |

*Assignment of $^{13}C$ multiplicity made from DEPT spectra.

1); in particular, the presence of a strong correlation between H-3 and H-2′/H-6′ is only possible for the *cis*-isomer of **1**. Compound **1** from *A. cochinchinensis* should therefore be assigned the planar *cis*-structure accorded to (−)-nyasol and, since its optical rotation is of opposite sign to the previously reported natural product [7], it must have inverted absolute stereochemistry at the C-3 chiral centre. We propose that **1** be named (+)-nyasol.

From the foregoing analysis, it seems likely that the natural product hinokiresinol in fact shares the same *cis*-stereochemistry as that now confirmed by NOESY for nyasol, since they both share the same value for the $J_{1,2}$ coupling constant in NMR. We propose that the structure of hinokiresinol should be revised to be *cis* as for nyasol. Given the available evidence it is certainly not the case, as suggested in a recent compilation of natural products [12], that the structure of nyasol should be revised to that of hinokiresinol.

## EXPERIMENTAL

*General.* Chemical shifts are expressed in $\delta$ relative to TMS as int. standard. All NMR expts were run on Bruker DPX 300 or DRX 500 instruments. Two dimensional spectra were recorded with 1024 data points in $F_2$ and 256 data points in $F_1$. MS were recorded in EI mode at 70 eV. IR spectra were recorded in $CH_2Cl_2$.

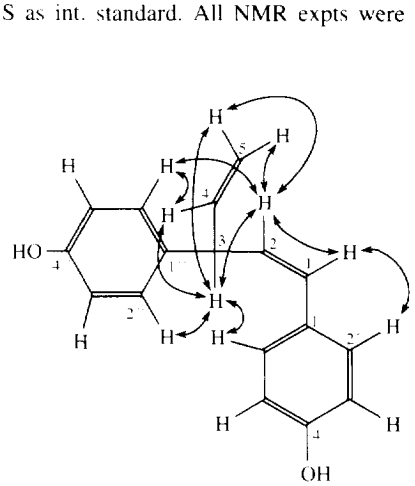


Fig. 1. NOESY correlations for compound **1**.

*Isolation of* **1**. Tubers were collected from Pokfulam Country Park, Hong Kong Island. A voucher specimen of *A. cochinchinensis* (Lour.) Merr. is deposited in the University of Hong Kong herbarium (GDBROWN 96/2). The sample (390 g) was immediately extracted with $CH_2Cl_2$ in a Soxhlet apparatus (8 hr). The organic extract was then dried and evapd under red. pres. to yield a yellow gum (4.26 g;1.1% w/w). **1** (8 mg) was isolated by CC ($R_f$ 0.21, 35% EtOAc in hexane, staining purple on TLC with *p*-anisaldehyde soln).

*(+)-Nyasol* (**1**). Oil. $[\alpha]_D$ +112° ($CH_2Cl_2$; *c* 0.4). MS *m/z* (rel. int.): 252.1151 [$M^+$, $\Delta$ − 0.1 mmu for $C_{17}H_{16}O_2$] (100), 237 (35), 158 (55), 145 (20), 129 (100), 107 (30), 77 (18). IR $\nu_{max}$ cm$^{-1}$ 3600, 3400 *br*, 1610, 1250. $^1H$ NMR ($CDCl_3$): $\delta$ 7.17 (2H, *d*, $J$ = 8.6 Hz), 7.10 (2H, *d*, $J$ = 8.6 Hz), 6.78 (2H, *d*, $J$ = 8.6 Hz), 6.77 (2H, *d*, $J$ = 8.6 Hz), 6.51 (1H, *d*, $J$ = 11.2 Hz), 6.00 (1H, *ddd*, $J$ = 17.5, 9.7, 5.9 Hz), 5.67 (1H, *dd*, $J$ = 11.2, 9.9 Hz), 5.17 (1H, *dd*, $J$ = 17.5, 1.5 Hz), 5.15 (1H, *dd*, $J$ = 9.7, 1.5 Hz), 4.98 (1H, *br s*, exch. $D_2O$, -OH), 4.85 (1H, *br s*, exch. $D_2O$, -OH), 4.51 (1H, *dd*, $J$ = 9.9, 5.9 Hz).

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