http://dx.doi.org/10.5012/bkcs.2013.34.4.1247

Synthesis of Naturally Occurring Norlignan (±)-Nyasol

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Received November 27, 2012, Accepted January 7, 2013

Key Words : Regiospecific epoxide opening, Lindlar catalyst, (±)-Nyasol

The norlignans including nyasol **1**,[1] hinokiresinol **2**, agatharesinol **3**,[2] sequirin C **4** and sugiresinol **5**[3] have received widespread interest as pharmaceutically valuable compounds, mainly because of their various clinically important biological activities: *e.g.* antiplasmodial activity,[1] antifungal activity,[4] anticancer activity,[5] antimalarial activity,[6] anti-oomycete activity,[7] and estrogen receptor binding activity.[8]

Nyasol is one of the naturally occurring norlignans, which constitute abundant classes of phenylpropanoids. Nyasol has been isolated from various species of plants (*Asparagus africanus*,[1] *Anemarrhena asphodeloides*,[4,5] *Asparagus officinalis*,[9] and *Asparagus cochinchinensis*[10]). Nyasol and hinokiresinol are geometrical isomers and the confusion concerning the nomenclature of the two compounds nyasol and hinokiresinol was settled by Oketch-Rabah *et al.*, who agreed that the *Z*-isomer should be named nyasol and the *E*-isomer hinokiresinol.[1]

In particular, nyasol shows various biological activities. For example, nyasol stimulated the proliferation of estrogen-dependent T47D breast cancer cells, and their stimulatory effects were blocked by an estrogen antagonist. In addition, nyasol showed binding affinity for the bovine uterine estrogen receptor, but (+)-nyasol was found to bind approximately seven times more strongly than (−)-nyasol.[8] It was reported that (−)-nyasol increases hexobarbital sleeping time in mice.[11] Nyasol was also reported to possess antifungal activity[4] and inhibit testosterone 5α-reductase.[12] Furthermore, nyasol was found to exhibit antioxidant and antiatherogenic activities.[13]

These results have encouraged us to complete adaptable and scalable total synthesis of these classes of natural products for further pharmacological study. So far, hinokiresinol derivatives have been easily prepared from chalcones by using reduction and dehydration.[6] However, few successful synthetic procedures for nyasol have been reported other than the recent report by the Hoveyda group, which limits a scalable synthesis of nyasol.[14] Quan *et al.* also reported an approach to synthesis of di-*O*-methyl ethers of (+)-nyasol and related norlignans, however, they might fail deprotection of the methyl ethers to obtain the final nyasol since there

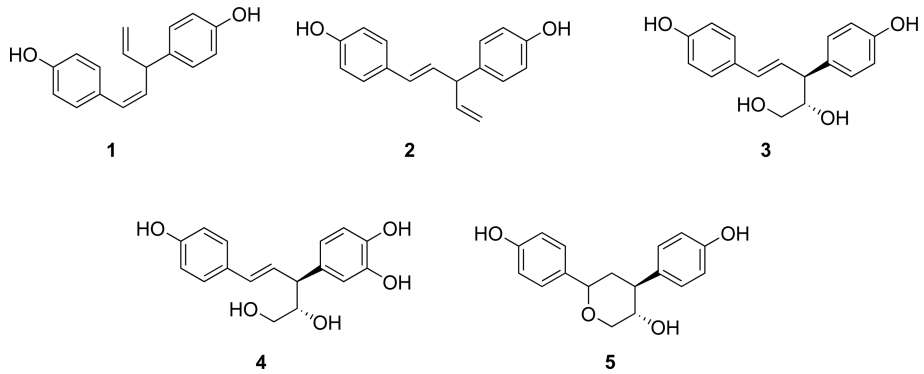


Figure 1. Structures of norlignans.

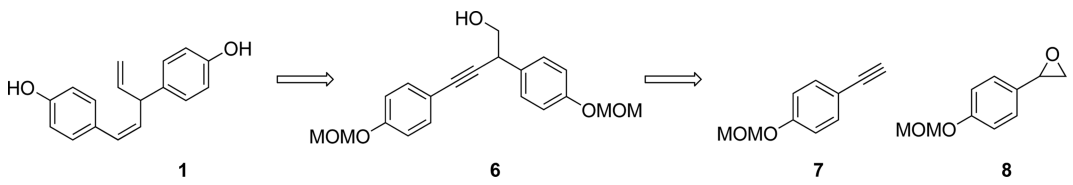
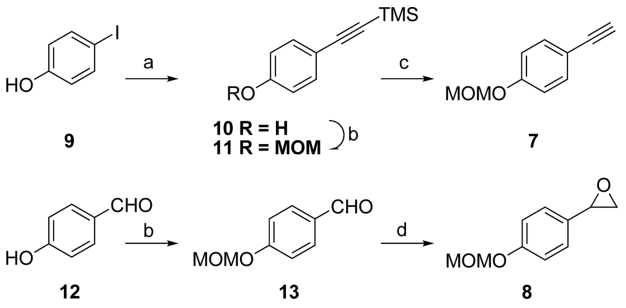


Figure 2. Retrosynthetic analysis for nyasol.

[a]These authors contributed equally to this work.



Scheme 1. Reagents and conditions: (a) $PdCl_2(PPh_3)_2$, CuI, TMS-acetylene, DIPEA, toluene, rt, 24 h, quant.; (b) MOMCl, DIPEA, CH_2Cl_2, 0 °C - rt, 4-12 h, 91-98%; (c) TBAF, THF, 0 °C - rt, 3 h, 98%; (d) 60% NaH, $(CH_3)_3SOI$, DMSO, 30 min, 56%.

was no report on deprotection step and physical properties for nyasol.[15] We assumed that harsh conditions to deprotect di-*O*-methyl ethers of (+)-nyasol might cause decomposition of the final product. Similarly, we failed the deprotection of di-*O*-methyl ethers of (±)-nyasol (data not shown). Herein, we describe a simple and efficient synthesis of (±)-nyasol **1** from commercially available 4-iodophenol and 4-hydroxybenzaldehyde.

The retrosynthesis makes fragments **7** and **8**, then regiospecific opening of styrene epoxide with phenyl acetylene was carried out to afford intermediate **6**. Reduction of **6** with Lindlar catalyst, followed by oxidation, Wittig reaction, and deprotection of MOM group allowed the final product (±)-nyasol **1** (Figure 2).

Fragment **7** was then obtained using Sonogashira coupling between the commercially available 4-iodophenol **9** and trimethylsilylacetylene.[16] Then MOM protection was followed by removal of the trimethylsilyl protecting group with TBAF. Compound **8** could be achieved by MOM protection of 4-hydroxybenzaldehyde followed by epoxidation using trimethylsulfoxonium iodide by the Corey method (Scheme 1).[17]

In order to obtain (±)-nyasol **1**, styrene epoxide **8** was coupled with phenyl acetylene **7** by regiospecific opening.[18] The homopropargylic alcohol **6** was then protected with TBS, followed by partial hydrogenation using Lindlar conditions to afford the required *cis*-isomer **15**. The reaction time was carefully optimized to avoid over-reduction to the alkane. The silyl ether group of **15** was deprotected with TBAF, and Dess-Martin oxidation[19] furnished the required aldehyde **17**. This intermediate **17** underwent Wittig reaction followed by deprotection of two MOM groups with diluted HCl in MeOH/H_2O to produce the (±)-nyasol **1**.[20] The geometry of the double bonds was confirmed by its magnitude coupling constants, which were matched with reported one (Scheme 2).

In conclusion, we have developed a new methodology for the synthesis of biologically important norlignans, (±)-nyasol. Our approach allowed for an efficient and economical method for a gram-scale synthesis of nyasol for animal study. Furthermore, this approach can be easily applied to an enantioselective synthesis of the racemic mixture. We are currently in the process of carrying out asymmetric synthesis *via* the Sharpless asymmetric epoxidation protocol and the enantiomers of nyasol will be useful in elucidating the stereochemical influence of their pharmacological activities.

Acknowledgments. This research was supported by the Korea Health Technology R&D Project, the Ministry of Health & Welfare (#A100766 to W-K. K) and by the Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education, Science and Technology (#2011-0026325 to Y. C), Republic of Korea.

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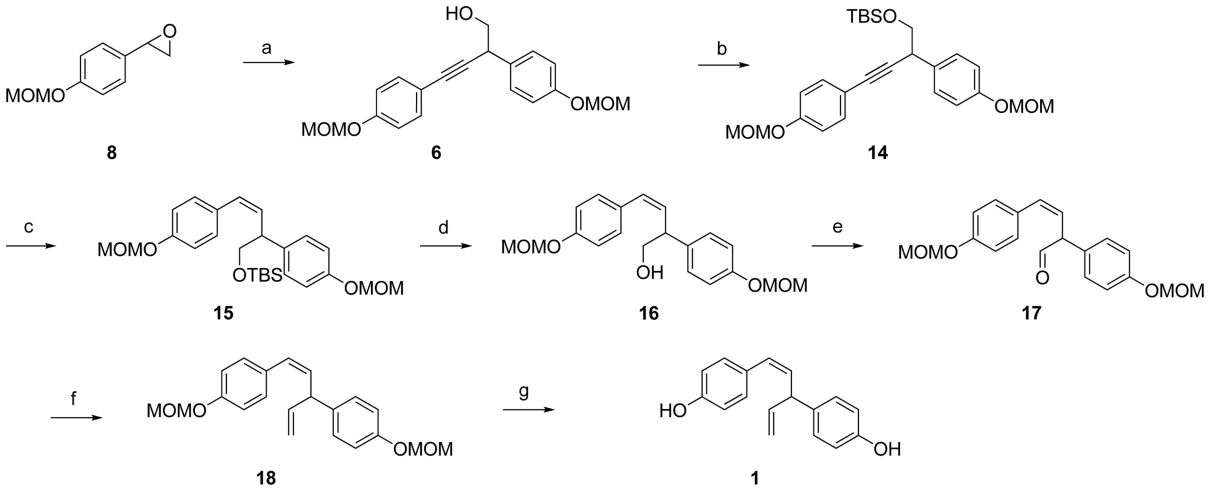

Scheme 2. Reagents and conditions: (a) *n*-BuLi, $BF_3{\cdot}OEt_2$, **7**, −50 °C, 3 h, 47%; (b) TBSCl, imidazole, CH_2Cl_2, 0 °C - rt, 1 h, 96%; (c) Lindlar cat., quinoline, 2 h, quant; (d) TBAF, THF, 0 °C, 3 h, 98%; (e) Dess-martin periodinane, CH_2Cl_2, 0 °C - rt, 1 h, 56%; (f) $Ph_3P^+CH_3I^-$, *n*-BuLi, THF, 0 °C, 10 min, 67%; (g) MeOH:H_2O (4:1), 1 N-HCl, 12 h, 80%.

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20. ^{1}H and ^{13}C NMR data of (±)-nyasol (**1**): ^{1}H-NMR (CD_3OD, 500 MHz) δ 7.13 (2H, d, J = 8.3 Hz, Ar-**H**), 7.02 (2H, d, J = 8.3 Hz, Ar-**H**), 6.74 (2H, d, J = 8.8 Hz, Ar-**H**), 6.73 (2H, d, J = 8.3 Hz, Ar-**H**), 6.47 (1H, d, J = 11.2 Hz, Ar-C**H**=CHCH(CH=CH_2)-Ar), 6.00 (1H, m, Ar-CH=CHCH(C**H**=CH_2)-Ar), 5.63 (1H, dd, J = 11.7, 9.7 Hz, Ar-CH=C**H**CH(CH=CH_2)-Ar), 5.11 (2H, m, Ar-CH=CHCH(CH=C$\mathbf{H}_2$)-Ar), 4.45 (1H, t, J = 8.8 Hz, Ar-CH=CHC**H**(CH=CH_2)-Ar); ^{13}C-NMR (CD_3OD, 75 MHz): 157.84, 156.93, 142.76, 135.75, 132.49, 130.96, 129.97, 129.69, 116.32, 116.00, 114.79, 48.47; MS (ESI): *m/z* 252 (M+).