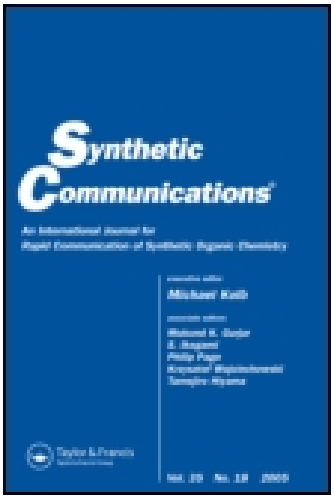

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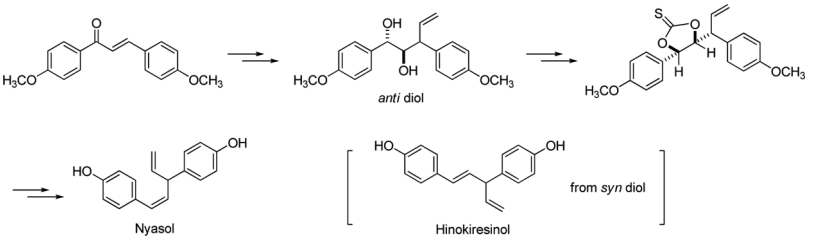
GRAPHICAL ABSTRACT



Abstract *A practical total synthesis of racemic nyasol (**7**) was explored. The α-hydroxyketo compound **3** was prepared from commercially available starting materials in two steps. Chelation-controlled reduction of the α-hydroxyketo compound **3** with $Zn(BH_4)_2$ gave the anti-1,2-diol compound **4** as the major product (*anti/syn = *11.5:1). Stereospecific elimination reaction of a 1,3-cyclic thionocarbonate intermediate (**5**) exclusively yielded the Z-alkene compound **6**. Our total synthesis is very concise (seven steps), uses commercially available starting materials, and offers good overall yield (40%).*

Keywords *Anti*-diol; chelation-controlled reduction; 1,3-cyclic thionocarbonate intermediate; (±)-nyasol; stereospecific *cis*-elimination

INTRODUCTION

Norlignans are naturally occurring pharmaceutically important compounds that possess diphenylpentane backbone structures. Nyasol and hinokiresiol (Fig. 1) are two typical compounds in this family. Two compounds have stereoisomeric relationships in their structures. Nyasol, the *Z*-stereoisomer of hinokiresinol, is an important norlignan compound isolated from many medicinal plants[1a–1f] and possesses diverse clinically valuable bioactivities such as anti-oomycete,[1a] anti-allergic,[1f] anti-atherogenic,[1g] antileishmanic,[2a] estrogen-like,[2b] anti-angiogenic,[2c] anti-oxidant,[2d] and anti-ischemic[2e] activities.

(±)-Nyasol was isolated from the methanol extract of *Anemarrhena asphodeloides* rhizomes.[1a] Nyasol effectively inhibited mycelial growth of *Colletotrichum orbiculare*,

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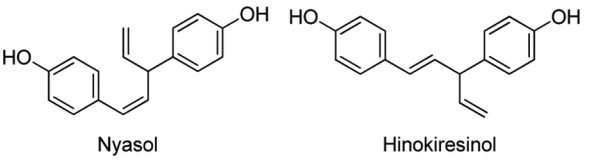


Figure 1. Structures of nyasol and hinokiresinol.

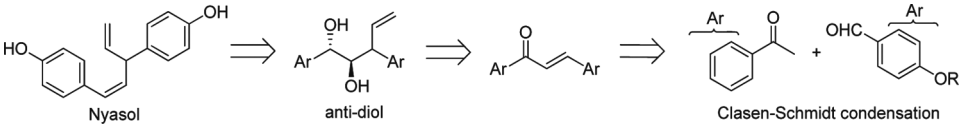
P. capsici, *Pythium ultimum*, *R. solani*, and *Cladosporium cucumerinum* in a range of 1–50 mg/ml, but did not affect the growth of bacteria and yeast. Recently (–)-nyasol has been reported to suppress neuroinflammatory response through the inhibition of nitric oxide (NO), prostaglandin E_2 (PGE_2), tumor necrosis factor (TNF)-α, and interleukin (IL)-1β. (–)-Nyasol inhibits the production of NO and PGE_2 by suppressing the expression of inducible nitric oxide synthase (*i*NOS) and cyclooxygenase-2 (COX-2). Further research on mode of action suggested that (–)-nyasol can modulate neuroinflammatory responses induced by microglial activation.[3]

However, because of the rarity of the amount, complicated and time-consuming isolation and purification procedures, and prohibitive cost to obtain bioactive substances from natural products, development of a synthetic procedure is required to support a sizable amount of sample for further biological evaluations. Therefore, we aimed to develop a practical and efficient total synthesis of hinokiresinol and nyasol. Hinokiresinol, the *E*-stereoisomer of nyasol, is relatively easy to synthesize from commercial starting materials in comparison with nyasol. Chalcone formation from 4′-methoxyacetophenone and *p*-anisaldehyde under Claisen–Schmidt conditions followed by vinyl addition, reduction, and dehydration steps provided a hinokiresinol precursor with high *E*-stereoselectivity.[4]

Several synthetic procedures for nyasol have been published.[5–8] Hoveyda's group[6] reported a methodology for synthesis of Z/E alkenes using vinyl aluminum reagents and a copper catalyst. Carreira's group[7] developed a more concise synthetic procedure via iridium-catalyzed substitution reactions between vinyl trifluoroborates and allyl alcohols. However, costly catalysts needed for these procedures are not suitable for practical large-scale nyasol synthesis. Recently Choi's group[8] reported a scalable synthesis of racemic nyasol; however, long reaction steps were required and the yield of (±)-nyasol was poor. We explored more concise and practical synthetic procedures to obtain a sizable amount of (±)-nyasol.

RESULTS AND DISCUSSION

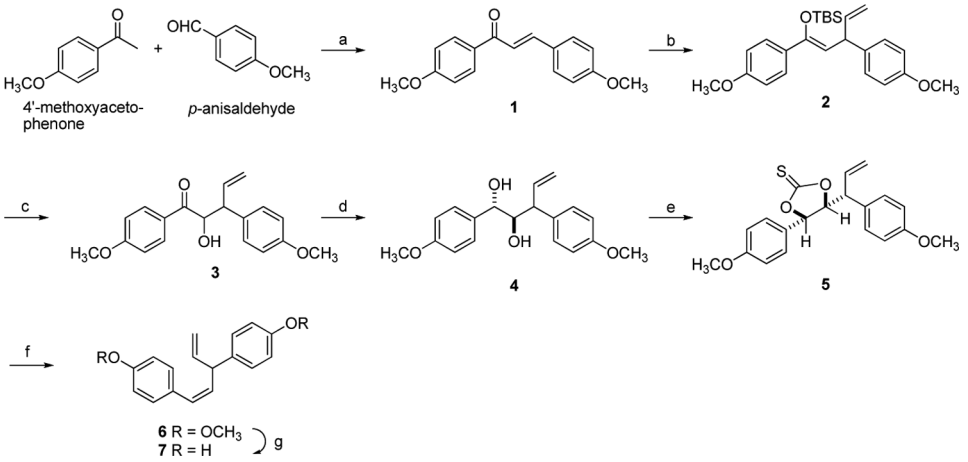
Our strategy for (±)-nyasol synthesis was as follows (Scheme 1): stereospecific *cis*-elimination reaction of the 1,3-cyclic thionocarbonate intermediate yields exclusively a *Z*-alkene via Corey–Winter olefin synthesis. An *anti*-1,2-diol could be prepared via chelation-controlled reduction of an α-hydroxyketo compound. An α,β-unsaturated ketone compound would be generated from 4′-methoxyacetophenone and *p*-anisaldehyde and converted to an α-hydroxyketo compound via Michael addition and Rubottom oxidation reaction.[9–11]



Scheme 1. Retrosynthetic analysis of (±)-nyasol.

The overall procedure for (±)-nyasol preparation is outlined in Scheme 2. A reaction between 4′-methoxyacetophenone and *p*-anisaldehyde (Claisen–Schmidt condensation) gave chalcone **1** as a yellow solid in 95% yield. Vinyl addition and in situ silylation with (*tert*-butyldimethyl)silyl chloride (TBSCl) produced compound **2**, which was used for the subsequent reaction without further purification. Rubottom oxidation of the compound **2** with *m*-chloroperoxybenzoic acid (*m*CPBA) followed by desilylation with 48% aqueous HF solution produced α-hydroxyketo intermediate **3** as a colorless oil in 90% yield (three steps). Chelation-controlled reduction of compound **3** with $Zn(BH_4)_2$ gave the *anti*-1,2-diol compound **4** as the major product (*anti*/*syn* = 11.5:1) in 92% yield.[11] Using $NaB(OAc)_3H$ or $NaBH_4$ for reduction decreased the *anti*/*syn* ratios (Table 1).

Corey–Winter olefin synthesis of compound **4** using thiocarbodiimidazole (TCDI) and diisopropylethylamine (DIPEA) in dichloromethane afforded 1,3-cyclic thionocarbonate **5** in 72% yield. Elimination reactions of 1,3-cyclic thionocarbonates were reported to produce *cis*-alkenes almost stereospecifically.[9] The elimination reaction of compound **5** with trimethylphosphite produced compound **6** (84%) and its *E*-isomer (8%). By comparing the coupling constants of olefinic protons of the product **6** and its isomer, the *Z* ($J = 11.4$ Hz)/*E* ($J = 16.0$ Hz) ratio was identified



Scheme 2. Reagents and conditions: (a) KOH, EtOH, 95%; (b) vinylmagnesium bromide, CuBr-Me_2S, HMPA, TBSCl, THF, 3 h; (c) *m*CPBA, $NaHCO_3$, CH_2Cl_2, then HF, MeOH, 90% (3 steps); (d) $Zn(BH_4)_2$, Et_2O, 92%; (e) TCDI, DIPEA, CH_2Cl_2, reflux, 2 h, 72%; (f) $P(OMe)_3$, reflux, 1 d, 84%, $Z/E = 11.5$; (g) MeMgI, 160 °C, 150 mbar, 1 h, 82%.

Table 1. Results of chelation-controlled reduction

Entry	Reagent	Yield (%)[a]	Ratio of *anti*/*syn* diol[b]
1	$NaBH_4$	85	2.5:1
2	$NaB(OAc)_3H$	80	6.0:1
3	$Zn(BH_4)_2$	92	11.5:1

[a]Yield after chromatography.
[b]Based on the ratio between compound **6** and its *E*-stereoisomer.

as 11.5:1. Demethylation of compound **6** with MeMgI under reduced pressure (150 mbar) gave final product **7** (nyasol) in 82% yield.[12]

The stereochemistry of *anti*/*syn*-diol (compound **4**) and cyclic thionocarbonate (compound **5**) was difficult to determine, because the diastereoisomers of the compounds **4** and **5** were unable to completely separate and the peaks of hydrogens attached to C−O bonds (**4**: 4.12–4.48 ppm, **5**: 4.90–5.13 ppm) on ^{1}H NMR spectra were mixed together and the coupling constants could not be measured. The diastereoisomeric ratios of compound **4** and **5** were deduced from the ratio of the compound **6** and its *E*-stereoisomer, which could be identified by comparing the coupling constants in ^{1}H NMR as mentioned.

EXPERIMENTAL

All chemicals were obtained from commercial suppliers and used without further purification. All solvents used for reactions were freshly distilled from proper dehydrating agent under nitrogen gas. All solvents used for chromatography were purchased and directly applied without further purification. ^{1}H NMR spectra were recorded on a Bruker Avance 300 (300-MHz) and Bruker DPX 400 (400-MHz) spectrometers. Chemical shifts are reported in parts per million (ppm) downfield relative to tetramethylsilane as an internal standard. Peak splitting patterns are abbreviated as m (multiplet), s (singlet), bs (broad singlet), d (doublet), bd (broad doublet), t (triplet), dd (doublet of doublets), and ddd (doublet of double doublet). ^{13}C NMR spectra were recorded on a Bruker DPX 400 (100-MHz) spectrometer; fully decoupled and chemical shifts are reported in parts per million (ppm) downfield relative to tetramethylsilane as an internal standard. Mass spectra were recorded on a Voyager DE STR MALDI-TOF mass spectrometer. Analytical thin-layer chromatography (TLC) was performed using commercial glass plates with silica gel 60F 254 purchased from Merck.

(±)-(*4R,5S*)-4-(4-Methoxyphenyl)-5-(1-(4-methoxyphenyl)allyl)-1,3-dioxolane-2-thione (5)

TCDI (3.4 g, 19.08 mmol) and DIPEA (11.1 mL, 63.61 mmol) were added to a solution of the compound **4** (2.0 g, 6.36 mmol) in CH_2Cl_2 (40 mL). The reaction was refluxed for 2 h, and the product was extracted with CH_2Cl_2 (150 mL), washed with saturated brine (100 mL × 2), and dried with Mg_2SO_4. The organic layer was evaporated to obtain the crude product, which was purified by column chromatography (hexane/EtOAc = 4:1) to afford the compound **5** (1.63 g, 72%) as a light yellow

oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.81 (m, 4H, C2 and C6 Ar1 and Ar2), 6.74 (m, 2H, C3 and C5 Ar2), 6.59 (m, 2H, C3 and C5 Ar1), 5.98–6.11 (m, 1H, CH=CH_2), 5.54 (d, 1H, $J = 7.4$, CH=CH_2), 5.35 (dd, 1H, $J = 7.4$, 10.7, CH=CH_2), 5.13 (m, 1H, CHAr), 4.90 (m, 1H, CH), 3.82 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 3.27 (m, 1H, CHCH=CH_2); MS (MALDI-TOF): m/z $[M]^+$ 356.44.

(±)-(*Z*)-4,4′-(Penta-1,4-diene-1,3-diyl)bis(methoxybenzene) (6)

A solution of the compound **5** (1.50 g, 4.21 mmol) in $P(OMe)_3$ (2.5 mL) was refluxed for 24 h. The mixture was evaporated to obtain the crude product, which was purified by column chromatography (hexane/EtOAc = 10:1) to afford the compound **6** (994 mg, 85%) and *E*-stereoisomer (86 mg) as a light colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.21–7.24 (m, 2H, C2 and C6 Ar1), 7.14–7.18 (m, 2H, C2 and C6 Ar2), 6.83–6.88 (m, 4H, C3 and C5 Ar1 and Ar2), 6.53 (d, 1H, $J =$ 11.4, ArCH=CH), 5.98–6.07 (m, 1H, CH=CH_2), 5.69 (dd, 1H, $J = 10.0$, 11.4, ArCH=CH), 5.14–5.20 (m, 2H, CH=CH_2), 4.52 (dd, 1H, $J = 6.1$, 10.0, CHCH=CH_2), 3.79 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 159.0 (CHOCH_3), 158.6 (CHOCH_3), 141.2 (CH=CH), 135.9 (CH=CH_2), 132.1 (Ar), 130.2 (Ar), 130.1 (Ar), 129.1 (Ar), 129.0 (CH=CH), 115.4 (CH=CH_2), 114.4 (Ar), 114.1 (Ar), 55.7 (OCH_3), 55.6 (OCH_3), 47.3 (CH); HRMS (MALDI-TOF): m/z calculated $[M]^+$ 280.1463, observed $[M]^+$ 280.3867. *E*-Stereoisomer of compound **6**: ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.22–7.24 (m, 2H, C2 and C6 Ar1), 7.08–7.14 (m, 2H, C2 and C6 Ar2), 6.75–6.84 (m, 4H, C3 and C5 Ar1 and Ar2), 6.29 (d, 1H, $J = 16.0$, ArCH=CH), 6.12–6.20 (dd, 1H, $J = 6.6$, 16.0, ArCH=CH), 5.96–6.07 (m, 1H, CH=CH_2), 5.00–5.13 (m, 2H, CH=CH_2), 4.08 (t, 1H, $J = 6.3$, CHCH=CH_2), 3.73 (s, 6H, OCH_3).

CONCLUSION

In conclusion, we have established an efficient and practical total synthesis of (±)-nyasol via chelation-controlled reduction of an α-hydroxyketo compound with $Zn(BH_4)_2$ and stereospecific *cis*-elimination of a 1,3-cyclic thionocarbonate intermediate as key reactions. Our total synthesis is very concise (seven steps), uses commercially available chemicals, and offers high overall yield (40%). The reaction of most reactions are adaptable to scalable processes and are therefore suitable for large-scale synthesis of (±)-nyasol. In addition, our method can be easily applied to synthesize optically active nyasol using chiral inducing agents. Currently we are investigating asymmetric Michael reaction using chiral ligands to obtain a chiral enol intermediate, which could allow us to produce optically active nyasol. Also, our synthetic procedure will be applied to prepare nyasol analogs for SAR study in the near future.

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SUPPLEMENTAL MATERIAL

Supplemental data for this article can be accessed on the publisher's website.

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