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Asymmetric Synthesis

A Facile Asymmetric Approach to the Multicyclic Core Structure of Mangicol A

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Abstract: Chiral propargylic ether-based triene–ynes are synthesized with high enantiomeric purity by employing an asymmetric enyne addition to aldehydes catalyzed by 1,1′-bi-2-naphthol in combination with $ZnEt_2$, $Ti(OiPr)_4$ and dicyclohexylamine at room temperature. These substrates are found to undergo a one-pot domino Pauson–Khand and Diels–Alder cycloaddition catalyzed by $[RhCl(CO)_2]_2$ under CO to generate a series of multicyclic products with high chemoselectivity and stereoselectivity. These products contain the multicyclic core structure of mangicol A which could facilitate the synthesis and study of this class of natural products.

Introduction

Mangicol A represents a new type of sesterterpenoids containing a tetracyclic skeleton and a quaternary chiral carbon core (Figure 1). It was isolated in 2000 by Fenical and his co-workers from the marine fungus *Fusarium heterosporum*.[1] Mangicol A and other members of this family of natural products have exhibited cytotoxic and anti-inflammatory activities. Several attempts have been reported for the synthesis of this class of compounds but no total synthesis has been achieved to date.[2–4] Uemura synthesized the polycyclic core structure of mangicols in 29 steps in 2004 by employing an intramolecular transannular Diels–Alder reaction of a macrocycle.[4]

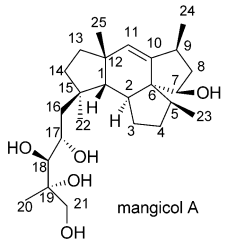
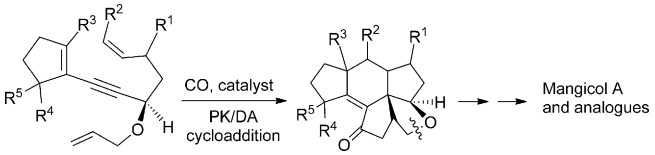


Figure 1. Mangicol A.

We propose a one-pot reaction to construct the tetracyclic core structure of mangicol A. As shown in Scheme 1, a catalytic Pauson–Khand (PK) cycloaddition of a chiral propargylic ether-based triene–yne followed by an intramolecular Diels–Alder (DA) reaction will be conducted to generate a pentacyclic product. Cleavage of the C–O bond of the hydrofuran ring of the pentacyclic product followed by functional group modification could eventually lead to mangicol A and its analogs. Since the chiral propargylic ether starting material containing three alkene functions could give more than one possible PK cyclization products, high chemoselectivity is required for the PK cycloaddition in the first step. After the PK/DA reactions, new chiral centers are generated. Thus, high stereoselectivity is also necessary in order to obtain the desired product. Recently, we have reported an initial test of this approach by conducting a domino PK/DA cycloaddition of an analog of the chiral propargylic ether starting material without the five-membered ring. This has led to the formation of a tetracyclic product.[5] In this paper, we report our further expansion of this strategy to prepare the pentacyclic products from the domino PK/DA cycloaddition. High chemoselectivity and stereoselectivity have been achieved for this efficient multicyclic construction.



Scheme 1. A proposed approach to the multicyclic core structure of mangicol A.

Results and Discussion

Preparation of the Chiral Propargylic Ethers by the Catalytic Asymmetric Alkyne Addition to Aldehydes

In order to prepare the chiral propargylic ether-based triene–ynes as the starting materials for the domino PK/DA cycloaddition, we have utilized a catalytic asymmetric method developed in our laboratory for the synthesis of chiral propargylic alcohols. Recently, we reported that the asymmetric reaction of terminal alkynes with aldehydes can be conducted at room temperature to generate chiral propargylic alcohols with high enantioselectivity by using a catalytic amount of 1,1′-bi-2-naphthol (BINOL) in combination with $Ti(OiPr)_4$, $ZnEt_2$ and dicyclohexylamine (Cy_2NH).[6–8] Scheme 2 summarizes the results

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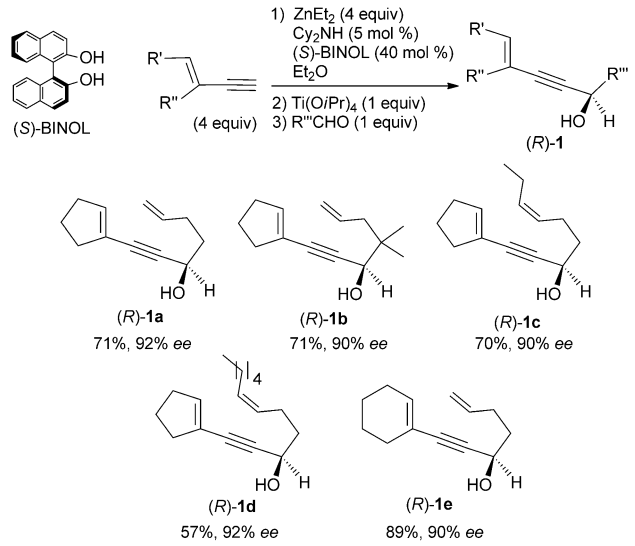
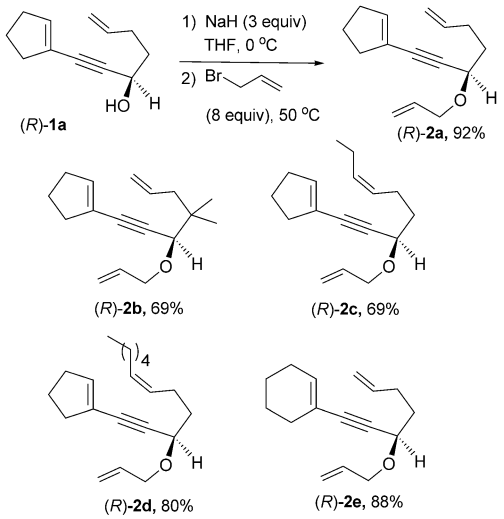
for the use of this catalytic method to prepare a series of chiral propargylic alcohols (*R*)-**1a**–**e** for the proposed cycloaddition. All these reactions were conducted in diethyl ether at room temperature under nitrogen in a three-step-one-pot process. In the first step, an enyne was treated with $ZnEt_2$ and Cy_2NH, which presumably generated a nucleophilic alkynyl zinc reagent. In this step, it is proposed that coordination of Cy_2NH with Et_2Zn could increase the basicity of the Et group on Zn to facilitate the deprotonation of the enyne. (*S*)-BINOL (40 mol%) was also added in the first step, which should be deprotonated by $ZnEt_2$. In the second step, $Ti(OiPr)_4$ was added. In this step, the combination of the deprotonated (*S*)-BINOL with $Ti(OiPr)_4$ could generate a chiral Lewis acid complex to catalyze the reaction. In the third step, an aldehyde was added and the asymmetric alkyne addition proceeded. After aqueous workup, a chiral propargylic alcohol product was obtained. In the second step, after the addition of $Ti(OiPr)_4$, additional time (3 h) was required in order to generate the BINOL-Ti^{IV} complex to control the stereochemistry of the next step. When the addition of $Ti(OiPr)_4$ was immediately followed with the addition of the aldehyde, enantioselectivity was much lower. As shown in Scheme 2, these catalytic asymmetric enyne additions to the aliphatic aldehydes were accomplished with 57–89% yield and 90–92% *ee*. The configurations of the chiral propargylic alcohols were determined on the basis of our previous studies.[6]



Scheme 2. Catalytic asymmetric alkyne addition to aldehydes to form chiral propargylic alcohols.

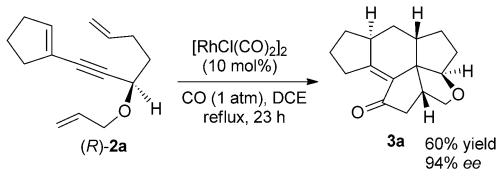
The chiral propargylic alcohols (*R*)-**1a**–**e** are converted to the corresponding allylic ethers as shown in Scheme 3. Treatment of the chiral propargylic alcohols with NaH at 0 °C followed by reactions with allyl bromide at 50 °C gave the desired propargylic ethers in 69–92% yields.



Scheme 3. Preparation of the chiral propargylic ether-based triene–ynes.

Catalytic Domino PK/DA Cycloaddition

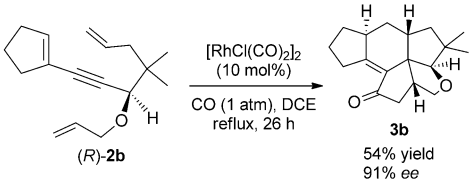
When the solution of (*R*)-**2a** in 1,2-dichloroethane (DCE) was heated in the presence of 10 mol% $[RhCl(CO)_2]_2$ under 1 atm CO, a domino PK/DA cycloaddition occurred to generate the pentacyclic product **3a** with 60% yield and 94% *ee* (Scheme 4).[9–11] Thus a highly chemoselective and stereoselective transformation has taken place. The enantiomeric purity of the original propargylic alcohol generated by the catalytic asymmetric enyne addition to aldehydes has been preserved in this domino cycloaddition process. In this conversion, the original propargylic chiral center has directed the formation of four additional chiral centers. The structure of **3a** was established by high-resolution mass spectroscopic analysis and various ^1H and ^{13}C NMR spectroscopic analysis including COSY, NOESY, HSQC and DEPT-135 (see Supporting Information).



Scheme 4. Catalytic conversion of (*R*)-**2a** to generate **3a**.

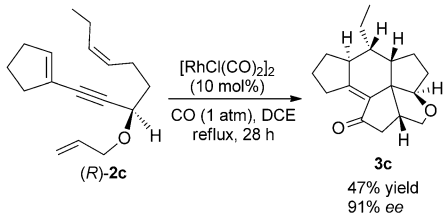
Similar to the conversion of (*R*)-**2a** to **3a**, when the triene–yne (*R*)-**2b** was treated with $[RhCl(CO)_2]_2$ and CO, compound **3b** was obtained with 54% yield and 91% *ee* (Scheme 5). The geminal dimethyl groups in (*R*)-**2b** did not have much effect on the cycloaddition. The stereochemistry of **3b** was assigned by comparing its NMR spectra with those of **3a**.

The propargylic ether (*R*)-**2c** contains a *cis* double bond in the alkyl chain. When this compound was subjected to the same catalytic conditions, the pentacyclic product **3c** was obtained as a single diastereomer with 47% yield and 91% *ee*



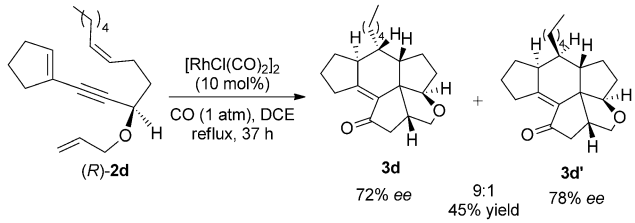
Scheme 5. Catalytic conversions of (*R*)-**2b**.

(Scheme 6). The ethyl group on the *cis* double bond of (*R*)-**2c** is located on the α face of the six-membered ring of **3c**. The structure of **3c** was determined by high-resolution mass spectroscopic analysis and various ^{1}H and ^{13}C NMR spectroscopic analysis including COSY, NOESY, HSQC and DEPT-135 (see Supporting Information).



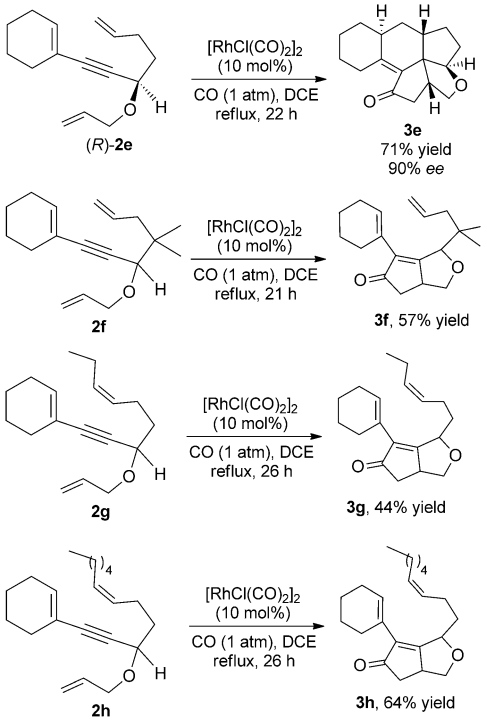
Scheme 6. Catalytic conversion of (*R*)-**2c**.

Compound (*R*)-**2d** contains a longer chain alkyl substituent on the *cis* double bond than (*R*)-**2c**. When (*R*)-**2d** was treated with $[RhCl(CO)_2]_2$ under CO, two diastereomers (9:1) were formed in 45% yield (Scheme 7). The major product **3d** contains a pentyl group on the α face of the six-membered ring. The factors contributed to the reduced enantiomeric purities of **3d** and **3d′** relative to the propargylic alcohol starting material are not clear at this stage. The more extended reaction time might be partially responsible.



Scheme 7. Catalytic conversion of (*R*)-**2d**.

Unlike compounds (*R*)-**2a**–**d**, the chiral propargylic ether (*R*)-**2e** contains a cyclohexene unit rather than a cyclopentene unit. This compound undergoes the same domino PK/DA reaction smoothly to give **3e** with 71% yield and 90% *ee* (Scheme 8). We also prepared the cyclohexene-containing racemic propargylic ethers **2f**, **2g** and **2h**. When these compounds were subjected to the conditions of the Rh^{I} catalysis in the conversion of (*R*)-**2e** to **3e**, only the PK cycloaddition products



Scheme 8. Catalytic conversions of (*R*)-**2e** and its racemic analogues **2f**–**h**.

3f, **3g** and **3h** were obtained in 57, 44 and 64% yield, respectively (Scheme 8). No intramolecular DA reaction took place. When the isolated **3g** was treated with $[Rh(CO)_2Cl]_2$ (10 mol%) under N_2 in refluxing toluene, there was still no DA reaction. Apparently, the intramolecular DA reaction is very sensitive to the sterics of the dienophiles in these compounds. This is in sharp contrast to the cyclopentene-containing substrates (*R*)-**2a**–**d**.

On the basis of the previous studies on the Rh-catalyzed PK and DA reactions,[10–12] the intermediates such as **4a** and **5a** from the reaction of (*R*)-**2a** are proposed to account for the stereoselectivity of this catalytic process (Figure 2). (*R*)-**2a** can coordinate with the metal center of the catalyst to generate the chair-like intermediate **4a**. The oxidative coupling of the coordinated triple bond and double bond of **4a** followed by CO insertion and reductive elimination would give the PK cyclization intermediate **5a**. Thus, the chair-like coordination of Rh in **4a** should lead to the *trans* arrangement for H_α and H_β in **5a**. The coordination of the diene unit and alkene unit to the Rh center in **5a** could promote an *exo* DA cycloaddition to generate the pentacyclic product **3a** with the observed *trans* arrangement of H_γ and H_δ. Previously, we have demonstrated that in the absence of the Rh^{I} complex, there was no intramolecular DA reaction for the isolated PK cycloaddition product.[5] For compounds **1c**,**d** that contains an ethyl or pentyl group on the dienophile double bond, the intermediates **5c**,**d** could form. The Rh^{I}-mediate *exo* DA cycloaddition of **5c**,**d** would give the obtained products **3c**,**d** with the R group of the major diastereomer *trans* to H_γ.

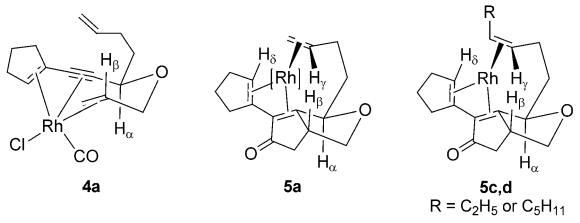


Figure 2. Proposed intermediates for the Rh^{I}-catalyzed domino reaction.

Conclusion

Using the chiral propargylic alcohols prepared from the asymmetric enyne addition to aliphatic aldehydes catalyzed by the BINOL/Ti(O*i*Pr)$_4$/Et$_2$Zn/Cy$_2$NH catalyst system, we have prepared a series of chiral propargylic ether-based triene–ynes with high enantiomeric purity. We have found that these compounds can undergo an efficient one-pot Rh^{I}-catalyzed domino PK/DA cycloaddition to generate multicyclic products with high chemoselectivity and stereoselectivity. These products contain the core structure of mangicol A which could facilitate the synthesis and study of this class of natural products.

Experimental Section

General Data

All commercial chemicals were used without further purification unless otherwise noted. All catalysts were purchased and stored under dry nitrogen atmosphere. Tetrahydrofuran was distilled over sodium and benzophenone under nitrogen. Diethyl ether and methylene chloride were dried by passing through activated alumina columns under nitrogen. All the NMR spectra were obtained in $CDCl_3$ unless indicated otherwise.

General procedure for the preparation of racemic propargylic alcohols from enyne addition to aldehydes

Under nitrogen, an enyne (1.5 equiv) was dissolved in THF (5 mL) and cooled to −78 °C. *n*BuLi (2.5 M in hexane, 1.2 equiv) was added and the mixture was stirred for 30 min. Then an aldehyde (0.5 mmol, 1 equiv) was added and the mixture was stirred for 3 h. Afterwards, the reaction mixture was warmed up to room temperature and quenched with the addition of saturated aqueous ammonium chloride solution. After extraction with CH_2Cl_2 for three times, the combined organic layer was washed with brine, dried with Na_2SO_4, concentrated by rotary evaporation and purified by column chromatography on silica gel eluted with hexanes/ethyl acetate to give the product.

General procedure for the (*S*)-BINOL-catalyzed enantioselective enyne addition to aldehydes

Under nitrogen, (*S*)-BINOL (40%) was weighted into a tared flask and dissolved in Et_2O (3 mL). An enyne (4 equiv), Cy_2NH (5%) and Et_2Zn (4 equiv) were added and the mixture was stirred at room temperature for 16 h. Then, Ti(O*i*Pr)$_4$ (100%) was added and the stirring continued for 3 h. An aldehyde (0.25 mmol, 1 equiv) was added and the mixture was stirred for another 4 h. The reaction was quenched with saturated aqueous ammonium chloride and extracted three times with CH_2Cl_2. The organic layer was dried with anhydrous Na_2SO_4 and concentrated by rotary evaporation. The resultant oil was purified by flash column chromatography on silica gel eluted with hexanes/ethyl acetate to give the product with 57–89% yield and 90–92% *ee*.

Characterizations of the optical active propargylic alcohols generated from the enyne additions to aldehydes

(*R*)-1-(Cyclopent-1-en-1-yl)hept-6-en-1-yn-3-ol [(*R*)-1 a]: Yellow oil, 31.1 mg, 71% yield. 92% *ee* determined by HPLC analysis: Chiralpak OD column, 98:2 hexanes/*i*PrOH, flow rate = 1.0 mL min^{-1}, λ = 254 nm, retention time: t_{major} = 11.0 min, t_{minor} = 13.1 min; $[\alpha]_D^{24}$ = −19.0 (c = 0.455, $CHCl_3$): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.03 (t, 1H, J = 2.1 Hz), 5.84 (m, 1H), 5.06 (dd, 1H, J = 17.1, 1.8 Hz), 4.98 (d, 1H, J = 10.2 Hz), 4.52 (t, 1H, J = 6.3 Hz), 2.42 (m, 4H), 2.23 (m, 2H), 2.03 (s, 1H), 2.03–1.80 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 138.5, 138.0, 124.1, 115.4, 91.2, 82.7, 62.7, 37.1, 36.6, 33.4, 29.7, 23.5; HRMS [EI(TOF)] for $C_{12}H_{16}O$ [M^+]: m/z: calcd for: 176.1201; found: 176.1199.

(*R*)-1-(Cyclopent-1-en-1-yl)-4,4-dimethylhept-6-en-1-yn-3-ol [(*R*)-1 b]: Colorless oil, 36 mg, 71% yield. 90% *ee* determined by HPLC analysis: Chiralpak AD-H column, 98:2 hexanes/*i*PrOH, flow rate = 1.0 mL min^{-1}, λ = 225 nm, retention time: t_{major} = 8.4 min, t_{minor} = 9.4 min; $[\alpha]_D^{27}$ = −20.3 (c = 1.300, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.02 (t, 1H, J = 1.8 Hz), 5.84 (m, 1H), 5.08 (dd, 1H, J = 5.4, 0.6 Hz), 5.04 (s, 1H), 4.19 (d, 1H, J = 6 Hz), 2.42 (m, 4H), 2.14 (m, 2H), 1.90 (m, 3H), 0.97 (s, 3H), 0.96 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 138.2, 135.2, 124.2, 117.9, 90.0, 83.7, 70.9, 43.0, 39.1, 36.6, 33.4, 23.5, 22.9, 22.8; HRMS [EI(TOF)] for $C_{14}H_{20}O$ [M^+]: m/z: calcd for: 204.1514; found: 204.1513.

(*R*,*Z*)-1-(Cyclopent-1-en-1-yl)non-6-en-1-yn-3-ol [(*R*)-1 c]: Colorless oil, 35.5 mg, 70% yield. 90% *ee* determined by HPLC analysis: Chiralpak OD column, 97:3 hexanes/*i*PrOH, flow rate = 1.0 mL min^{-1}, λ = 220 nm, retention time: t_{major} = 10.8 min, t_{minor} = 12.5 min; $[\alpha]_D^{27}$ = −28.7 (c = 1.275, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.02 (m, 1H), 5.37 (m, 2H), 4.51 (m, 1H), 2.41 (m, 4H), 2.20 (m, 2H), 2.04 (m, 3H), 1.88 (m, 2H), 1.76 (m, 2H), 0.95 (t, 3H, J = 7.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 138.4, 133.0, 128.0, 124.2, 91.3, 82.6, 62.8, 37.9, 36.6, 33.4, 23.5, 23.2, 20.8, 14.6; HRMS [EI(TOF)] for $C_{14}H_{20}O$ [M^+]: m/z: calcd for: 204.1514; found: 204.1512.

(*R*,*Z*)-1-(Cyclopent-1-en-1-yl)dodec-6-en-1-yn-3-ol [(*R*)-1 d]: Colorless oil, 35.2 mg, 57% yield; 92% *ee* determined by HPLC analysis: Chiralpak OD column, 97:3 hexanes/*i*PrOH, flow rate = 1.0 mL min^{-1}, λ = 225 nm, retention time: t_{major} = 10.7 min, t_{minor} = 12.8 min; $[\alpha]_D^{27}$ = −25.4 (c = 1.760, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.03 (s, 1H), 5.39 (m, 2H), 4.51 (m, 1H), 2.42 (m, 4H), 2.21 (m, 2H), 2.06 (m, 2H), 1.89 (m, 3H), 1.78 (m, 2H), 1.29 (m, 6H), 0.88 (t, 3H, J = 5.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 138.4, 131.5, 128.5, 124.1, 91.3, 82.6, 62.9, 38.0, 36.6, 33.4, 31.8, 29.6, 27.4, 23.5, 23.3, 22.8, 14.3; HRMS [EI(TOF)] for $C_{17}H_{26}O$ [M^+]: m/z: calcd for: 246.1984; found: 246.1980.

(*R*)-1-(Cyclohex-1-en-1-yl)hept-6-en-1-yn-3-ol [(*R*)-1 e]: Colorless oil, 42.4 mg, 89% yield; 90% *ee* determined by HPLC analysis: Chiralpak OD column, 95:5 hexanes/*i*PrOH, flow rate = 1.0 mL min^{-1}, λ = 225 nm, retention time: t_{major} = 8.5 min, t_{minor} = 9.8 min; $[\alpha]_D^{24}$ = −14.6 (c = 2.120, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.09 (m, 1H), 5.83 (m, 1H), 5.08 (dd, 1H, J = 18.9, 1.8 Hz), 4.98 (dd, 1H, J = 10.2, 1.8 Hz), 4.49 (t, 1H, J = 6.6 Hz), 2.22 (m, 2H), 2.08 (m, 4H), 2.00 (s, 1H), 1.80 (m, 2H), 1.59 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 138.0, 135.5, 120.3, 115.4, 87.4, 87.2, 62.6, 37.2, 29.7, 29.4, 25.8, 22.5, 21.7; HRMS [EI(TOF)] for $C_{13}H_{18}O$ [M^+]: m/z: calcd for: 190.1358; found: 190.1360.

General procedure for preparation of the chiral propargylic alcohol-based triene–ynes

To a solution of NaH 60% w/w (3 equiv) in THF was added a chiral propargylic alcohol (1 equiv) in THF at 0 °C under nitrogen and stirred for 30 min. Then allyl bromide (8 equiv) was added and the mixture was warmed to 50 °C overnight. The reaction was quenched with saturated aqueous ammonium chloride solution at room temperature and extracted with CH_2Cl_2 three times. The organic layer was washed with brine, dried with Na_2SO_4, concentrated by rotary evaporation and purified by flash column chromatography on silica gel eluted with hexanes/ethyl acetate to give the product in 69–92% yield.

Characterization of the Optical Active Triene–ynes

(*R*)-1-(3-(Allyloxy)hept-6-en-1-yn-1-yl)cyclopent-1-ene [(*R*)-2a]: Prepared from (*R*)-**1a** (21.3 mg, 0.12 mmol), colorless oil, 24 mg, 92% yield; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.03 (t, 1H, J=1.8 Hz), 5.86 (m, 2H), 5.30 (dd, 1H, J=17.4, 1.5 Hz), 5.18 (d, 1H, J=9.3 Hz), 5.04 (dd, 1H, J=17.1, 1.5 Hz), 4.96 (d, 1H, J=11.1 Hz), 4.25 (m, 2H), 3.95 (dd, 1H, J=12.6, 6.3 Hz), 2.42 (m, 4H), 2.23 (m, 2H), 1.86 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 138.2, 138.0, 134.8, 124.3, 117.4, 115.2, 89.3, 83.5, 69.8, 68.9, 36.7, 35.2, 33.4, 29.8, 23.5; HRMS [EI(TOF)] for $C_{15}H_{19}O$ [$M-H^+$]: m/z: calcd for: 215.14360; found: 215.14395.

(*R*)-1-(3-(Allyloxy)-4,4-dimethylhept-6-en-1-yn-1-yl)cyclopent-1-ene [(*R*)-2b]: Prepared from (*R*)-**1b** (27 mg, 0.13 mmol), colorless oil, 21.5 mg, 69% yield; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.03 (m, 1H), 5.86 (m, 2H), 5.30 (m, 1H), 5.17 (m, 1H), 5.04 (m, 2H), 4.30 (ddt, 1H, J=12.9, 4.8, 1.8 Hz), 3.93 (m, 1H), 3.87 (s, 1H), 2.45 (m, 4H), 2.16 (m, 2H), 1.90 (m, 2H), 0.99 (s, 3H), 0,97 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 137.8, 135.3, 135.0, 124.5, 117.6, 117.0, 88.3, 84.3, 77.2, 70.3, 43.4, 38.7, 36.7, 33.4, 29.9, 23.5, 23.2; GCMS (EI) for $C_{17}H_{24}O$ [M^+]: m/z: calcd for: 244.37; found: 244.

(*R*,*Z*)-1-(3-(Allyloxy)non-6-en-1-yn-1-yl)cyclopent-1-ene [(*R*)-2c]: Prepared from (*R*)-**1c** (26 mg, 0.13 mmol), colorless oil, 24.4 mg, 80% yield; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.03 (m, 1H), 5.92 (m, 1H), 5.36 (m, 3H), 5.16 (m, 1H), 4.23 (m, 2H), 3.97 (ddt, 1H, J=12.6, 6.3, 1.2 Hz), 2.42 (m, 4H), 2.20 (m, 2H), 2.06 (m, 2H), 1.89 (m, 2H), 1.79 (m, 2H), 0.95 (t, 3H, J=7.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 138.1, 134.8, 132.8, 128.1, 124.3, 117.4, 89.5, 83.4, 69.8, 69.0, 36.6, 36.0, 33.4, 23.5, 23.3, 20.7, 14.6; HRMS [EI(TOF)] for $C_{17}H_{24}O$ [M^+]: m/z: calcd for: 244.1827; found: 244.1818.

(*R*,*Z*)-1-(3-(Allyloxy)dodec-6-en-1-yn-1-yl)cyclopent-1-ene [(*R*)-2d]: Prepared from (*R*)-**1d** (35.2 mg, 0.14 mmol), colorless oil, 27.8 mg, 69% yield; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.03 (m, 1H), 5.92 (m, 1H), 5.36 (m, 3H), 5.18 (m, 1H), 4.23 (m, 2H), 3.97 (ddt, 1H, J=12.6, 6.3, 1.2 Hz), 2.43 (m, 4H), 2.21 (m, 2H), 2.03 (m, 2H), 1.90 (m, 2H), 1.79 (m, 2H), 1.29 (m, 8H), 0.88 (t, 3H, J=6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 138.1, 134.8, 131.2, 128.6, 124.3, 117.3, 89.5, 83.4, 69.8, 69.1, 36.7, 36.0, 33.4, 31.8, 29.6, 27.4, 23.5, 23.4, 22.8, 14.3; HRMS [ESI(TOF)] for $C_{20}H_{30}ONa$ [M+Na^+]: m/z: calcd for: 309.2194; found: 309.2191.

(*R*)-1-(3-(Allyloxy)hept-6-en-1-yn-1-yl)cyclohex-1-ene [(*R*)-2e]: Prepared from (*R*)-**1e** (42.4 mg, 0.22 mmol), colorless oil, 45.1 mg, 88% yield; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.09 (m, 1H), 5.93 (m, 1H), 5.79 (m, 1H), 5.30 (m, 1H), 5.17 (m, 1H), 5.04 (m, 1H), 4.97 (m, 1H), 4.22 (m, 2H), 3.97 (ddt, 1H, J=12.6, 6.3, 1.2 Hz), 2.22 (m, 2H), 2.09 (m, 4H), 1.84 (m, 2H), 1.60 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 138.1, 135.1, 134.9, 120.4, 117.4, 115.2, 88.0, 85.4, 69.7, 68.9, 35.2, 29.8, 29.5, 25.8, 22.5, 21.7; HRMS [EI(TOF)] for $C_{16}H_{21}O$ [$M-H^+$]: m/z: cacld for: 229.1592; found: 229.1592.

Characterization of the Racemic Triene–ynes

1-(3-(Allyloxy)-4,4-dimethylhept-6-en-1-yn-1-yl)cyclohex-1-ene (2f): Prepared from **S4** (173.2 mg, 0.79 mmol), colorless oil, 187 mg, 91% yield; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.10 (m, 1H), 5.87 (m, 2H), 5.30 (m, 1H), 5.17 (m, 1H), 5.03 (m, 2H), 4.29 (ddt, 1H, J=12.9, 4.8, 1.5 Hz), 3.90 (m, 1H), 3.85 (s, 1H), 2.13 (m, 6H), 1.60 (m, 4H), 0.98 (s, 3H), 0.96 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 135.3, 135.1, 134.7, 120.7, 117.5, 116.9, 88.8, 84.4, 77.1, 70.2, 43.4, 38.7, 29.9, 29.6, 25.8, 23.5, 23.2, 22.5, 21.7; HRMS [ESI(TOF)] for $C_{18}H_{27}O$ [M+H^+]: m/z: calcd for: 259.2062; found: 259.2066.

(*Z*)-1-(3-(Allyloxy)non-6-en-1-yn-1-yl)cyclohex-1-ene (2g): Prepared from **S5** (167.8 mg, 0.77 mmol), colorless oil, 181.5 mg, 91% yield; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.09 (m, 1H), 5.91 (m, 1H), 5.35 (m, 2H), 5.29 (m, 1H), 5.17 (m, 1H), 4.27 (ddt, 1H, J=12.6, 5.1, 1.5 Hz), 4.18 (t, 1H, J=6.6 Hz), 3.96 (ddt, 1H, J=12.6, 6.3, 1.5 Hz), 2.21 (q, 2H, J=7.2 Hz), 2.08 (m, 6H), 1.78 (m, 2H), 1,61 (m, 4H), 0.95 (t, 3H, J=7.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 135.1, 134.9, 132.8, 128.1, 120.5, 117.3, 87.9, 85.6, 69.8, 69.0, 36.1, 29.5, 25.8, 23.3, 22.5, 21.7, 20.7, 14.6; HRMS [ESI(TOF)] for $C_{18}H_{27}O$ [M+H^+]: m/z: calcd for: 259.2062; found: 259.2061.

(*R*)-1-(3-(Allyloxy)dodec-6-en-1-yn-1-yl)cyclohex-1-ene (2h): Prepared from **S6** (205 mg, 0.79 mmol), light yellow oil, 157.8 mg, 67% yield; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.10 (m, 1H), 5.92 (m, 1H), 5.38 (m, 2H), 5.30 (m, 1H), 5.17 (m, 1H), 4.27 (ddt, 1H, J=12.6, 5.1, 1.5 Hz), 4.18 (t, 1H, J=6.6 Hz), 3.96 (ddt, 1H, J=12.3, 6, 1.2 Hz), 2.21 (q, 2H, J=6.9 Hz), 2.10 (m, 6H), 1.78 (m, 2H), 1,59 (m, 4H), 1.29 (m, 6H), 0.88 (t, 3H, J=6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 135.2, 134.9, 131.2, 128.7, 120.5, 117.3, 88.0, 85.6, 69.7, 69.0, 36.1, 31.8, 29.7, 29.5, 27.4, 25.8, 23.4, 22.8, 22.5, 21.7, 20.7, 14.3; HRMS [ESI(TOF)] for $C_{21}H_{33}O$ [M+H^+]: m/z: calcd for: 301.2531; found: 301.2532.

General Procedure for the Domino PK/DA Cycloaddition

Under nitrogen, a triene–yne (1 equiv) and $[Rh(CO)_2Cl]_2$ (0.1 equiv) were weighed into a tared two-necked round bottom flask and dissolved in DCE (3 mL). The flask was fitted with a reflux condenser fitted with a septum and the side arm of the flask was also fitted with a septum. The solution was bubbled with CO gas for 2 min through the side arm fitted with septum and a vent needle in the septum of the reflux condenser. Then, the solution was placed under CO atmosphere by using a balloon. After the reaction mixture was heated at 70 °C to reflux temperature for 21–37 h, it was cooled to room temperature and the CO was released cautiously in the hood. The reaction mixture was concentrated and the crude product was purified by column chromatography on silica gel eluted with hexanes/ethyl acetate to give the product in 45–71% yield and 71–94% *ee*.

Characterizations of the Domino PK/DA Cycloaddition Products 3a–e

3a: Prepared from (*R*)-**2a** (24 mg, 0.11 mmol), colorless oil, 16.3 mg, 60% yield; 94% *ee* determined by HPLC analysis: Chiralpak AD-H column, 98:2 hexanes/*i*PrOH, flow rate = 1.0 mL min^{-1}, λ = 254 nm, retention time: t_{major} = 22.8 min, t_{minor} = 14.6 min; $[\alpha]_D^{23}$ = −103.6 (c = 0.815, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): δ = 4.15 (m, 1H), 4.09 (dd, 1H, J=9, 4.2 Hz), 3.84 (d, 1H, J=9 Hz), 2.82 (dd, 1H, J=19.2, 8.4 Hz), 2.64 (m, 1H), 2.52 (m, 2H), 2.28 (m, 3H), 2,09 (m, 2H), 1.91 (dd, 1H, J=13.2, 4.8 Hz), 1.82 (m, 1H), 1.75 (m, 1H), 1.71–1.54 (m, 3H), 1.07 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 205.0, 160.6, 132.4, 91.2, 73.0, 62.9, 47.5, 43.1, 42.4, 39.8, 35.7, 32.8, 32.6,

32.0, 31.6, 24.9; HRMS [ESI(TOF)] for $C_{16}H_{21}O_2$ [M+H$^+$]: m/z: calcd for: 245.1542; found: 245.1544.

3b: Prepared from (*R*)-**2b** (21.5 mg, 0.09 mmol), light yellow oil, 13 mg, 54% yield; 91% *ee* determined by HPLC analysis: Chiralpak AD-H column, 95:5 hexanes/*i*PrOH, flow rate = 1.0 mL min^{-1}, λ = 254 nm, retention time: t_{major} = 7.1 min, t_{minor} = 6.4 min; $[\alpha]_D^{26}$ = −79.7 (c = 0.650, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): δ = 4.05 (m, 1H), 3.87 (d, 1H, J = 9 Hz), 3.76 (s, 1H), 2.83 (dd, 1H, J = 19.2, 8.4 Hz), 2.61 (m, 1H), 2.46 (m, 3H), 2.26 (m, 1H), 2.11 (m, 1H), 1.91 (m, 2H), 1.84 (m, 1H), 1.63 (m, 1H), 1,58 (m, 1H), 1.51 (m, 1H), 1.25 (m, 1H), 1.06 (s, 3H), 0.93 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 204.8, 158.7, 134.2, 96.2, 72.6, 64.0, 47.6, 45.9, 43.0, 40.9, 40.2, 38.3, 32.9, 32.7, 31.7, 29.1, 24.8, 24.5; HRMS [ESI(TOF)] for $C_{18}H_{25}O_2$ [M+H$^+$]: m/z: calcd for: 273.1855; found: 273.1850.

3c: Prepared from (*R*)-**2c** (24.4 mg, 0.10 mmol), light yellow oil, 12.7 mg, 47% yield; 91% *ee* determined by HPLC analysis: Chiralpak AD-H column, 98:2 hexanes/MeOH, flow rate = 1.0 mL min^{-1}, λ = 254 nm, retention time: $_{major}$ = 9.9 min, t_{minor} = 12.9 min; $[\alpha]_D^{24}$ = −84.2 (c = 0.635, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): δ = 4.21 (t, 1H, J = 5.4 Hz), 4.04 (dd, 1H, J = 4.5, 3.6 Hz), 3.86 (d, 1H, J = 9 Hz), 2.86 (dd, 1H, J = 20.4, 9 Hz), 2.52 (m, 3H), 2.30 (m, 2H), 2.11 (m, 2H), 1.88 (m, 1H), 1.82 (m, 2H), 1.61 (m, 3H), 1.48 (m, 1H), 1,28 (m, 1H), 1.01 (m, 2H), 0.94 (t, 3H, J = 7.2 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 205.4, 159.3, 133.9, 91.4, 72.3, 64.2, 47.3, 46.3, 44.9, 44.7, 43.5, 32.4, 32.3, 31.4, 25.3, 24.9, 24.5, 12.5; HRMS [ESI(TOF)] for $C_{18}H_{25}O_2$ [M+H$^+$]: m/z: calcd for: 273.1855; found: 273.1855.

3d: Prepared from (*R*)-**2d** (27.8 mg, 0.10 mmol), colorless oil, 13.6 mg, 45% yield, dr = 9:1. 72% *ee* determined by HPLC analysis: Chiralpak AD-H column, 99:1 hexanes/MeOH, flow rate = 1.0 mL min^{-1}, λ = 254 nm, retention time: t_{major} = 13.9 min, t_{minor} = 9.0 min; $[\alpha]_D^{24}$ = −105.3 (c = 0.530, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): δ = 4.20 (t, 1H, J = 10.2 Hz), 4.03 (m, 1H), 3.84 (d, 1H, J = 18 Hz), 2.86 (dd, 1H, J = 40.8, 17.4 Hz), 2.47 (m, 3H), 2.26 (m, 2H), 2.11 (m, 2H), 1.83 (m, 3H), 1.53 (m, 5H), 1.28 (m, 6H), 1.05 (m, 2H), 0.89 (t, 3H, J = 13.2 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 204.7, 158.6, 133.2, 90.7, 71.6, 63.5, 46.6, 44.5, 44.2, 43.7, 42.8, 32.0, 31.8, 31.7, 30.9, 30.6, 26.7, 24.5, 24.3, 22.5, 14.0; HRMS [ESI(TOF)] for $C_{21}H_{31}O_2$ [M+H$^+$]: m/z: calcd for: 315.2297; found: 315.2323.

3e: Prepared from (*R*)-**2e** (45.1 mg, 0.20 mmol), light yellow solid, 36 mg, 71% yield. 90% *ee* determined by HPLC analysis: Chiralpak AD-H column, 95:5 hexanes/*i*PrOH, flow rate = 1.0 mL min^{-1}, λ = 254 nm, retention time: t_{major} = 13.7 min, t_{minor} = 11.1 min; $[\alpha]_D^{25}$ = −81.4 (c = 1.800, $CHCl_3$); M.p. 74–75 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ = 4.21 (d, 1H, J = 4.8 Hz), 3.97 (dd, 1H, J = 9, 4.2 Hz), 3.82 (m, 1H), 3.76 (d, 1H, J = 9 Hz), 2.66 (dd, 1H, J = 19.2, 10.2 Hz), 2.46 (m, 1H), 2.18 (m, 3H), 2.01 (m, 2H), 1.85 (m, 2H), 1.74 (m, 3H), 1.61 (m, 1H), 1.50 (m, 2H), 1.28 (m, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 206.7, 154.0, 132.6, 90.0, 74.3, 62.6, 45.7, 44.7, 40.4, 37.6, 35.2, 34.4, 32.8, 32.7, 28.8, 27.5, 25.8; HRMS [ESI(TOF)] for $C_{17}H_{23}O_2$ [M+H$^+$]: m/z: calcd for: 259.1698; found: 259.1699.

Characterization of the PK Cycloaddition Products 3f–h

3f: Prepared from **2f** (187 mg, 0.73 mmol), light yellow solid, 117.4 mg, 57% yield; M.p. 67–68 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.79 (m, 1H), 5.69 (s, 1H), 5.06 (s, 1H), 5.01 (d, 1H, J = 8.4 Hz), 4.54 (s, 1H), 4.30 (t, 1H, J = 6.9 Hz), 3.14 (m, 2H), 2.61 (dd, 1H, J = 18, 6 Hz), 2.40 (d, 1H, J = 16.8 Hz), 2.05 (m, 5H), 1.61 (m, 4H), 1.23 (s, 1H), 0.89 (s, 3H), 0.87 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 208.3, 176.8, 140.5, 134.7, 130.1, 128.6, 118.0, 82.8, 71.7, 43.6, 43.5, 39.5, 29.9, 27.4, 25.4, 23.5, 23.4, 22.6, 22.0; HRMS [ESI(TOF)] for $C_{19}H_{27}O_2$ [M+H$^+$]: m/z: calcd for: 287.2011; found: 287.2006.

3g: Prepared from **2g** (90.8 mg, 0.35 mmol), colorless oil, 44 mg, 44% yield; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.17 (m, 1H), 5.37 (m, 2H), 4.74 (m, 1H), 4.31 (m, 1H), 3.19 (m, 2H), 2.65 (dd, 1H, J = 17.7, 6 Hz), 2.28–2.00 (m, 9H), 1.82–1.57 (m, 6H), 0.95 (t, 3H, J = 7.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 208.3, 176.7, 137.1, 133.2, 130.4, 129.2, 127.9, 76.1, 71.7, 42.4, 40.0, 35.9, 29.9, 27.8, 25.7, 23.4, 22.8, 22.0, 20.8, 14.5; HRMS [ESI(TOF)] for $C_{19}H_{27}O_2$ [M+H$^+$]: m/z: calcd for: 287.2011; found: 287.2007.

3h: Prepared from **2h** (78.9 mg, 0.30 mmol), colorless oil, 55 mg, 64% yield; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.18 (m, 1H), 5.39 (m, 2H), 4.74 (m, 1H), 4.31 (m, 1H), 3.19 (m, 2H), 2.65 (dd, 1H, J = 17.7, 6 Hz), 2.27–2.09 (m, 6H), 2.01 (m, 2H), 1.80–1.59 (m, 6H), 1.34–1.24 (m, 7H), 0.87 (t, 3H, J = 6.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 208.3, 176.7, 137.1, 131.6, 130.4, 129.2, 128.4, 76.1, 71.7, 42.4, 40.0, 35.9, 31.7, 29.9, 29.6, 27.8, 27.4, 25.7, 23.5, 22.8, 22.0, 14.3; HRMS [ESI(TOF)] for $C_{22}H_{33}O_2$ [M+H$^+$]: m/z: calcd for: 329.2481; found: 329.2480.

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Keywords: asymmetric synthesis · Diels–Alder reaction · mangicols · Pauson–Khand cyclization · propargylic alcohols

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FULL PAPER

Asymmetric Synthesis

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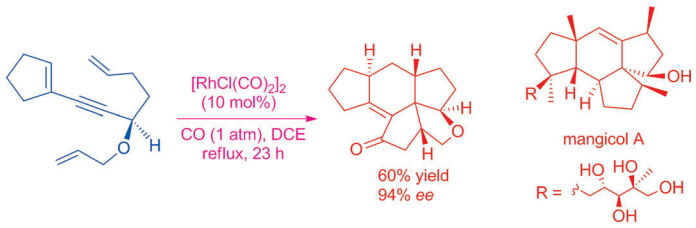
A Facile Asymmetric Approach to the Multicyclic Core Structure of Mangicol A



Chiral propargylic ether-based triene–ynes are found to undergo a one-pot domino Pauson–Khand and Diels–Alder cycloaddition catalyzed by $[RhCl(CO)_2]_2$ under CO to generate a series of multicyclic products with high chemoselectivity and stereoselectivity. These products contain the multicyclic core structure of mangicol A which could facilitate the synthesis and study of this class of natural products.