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Ring-Closing Strategy Utilizing Nitrile α-Anions: Chiral Synthesis of (+)-Norchrysanthemic Acid and Expeditious Asymmetric Total Synthesis of (+)-Grandisol

Tetsuya Fujiwara,[a] Tomohito Okabayashi,[a] Yuji Takahama,[a] Noritada Matsuo,[a] Yoo Tanabe*[a]

Abstract: Chiral syntheses of two distinct small cycloalkanes, (1*R*,3*R*)-(1*Z*)-norchrysanthemic acid and (+)-grandisol, were performed by characteristic ring-closing methodologies using carbanions at the α-position of nitriles (nitrile α-anions).
(i) (1*R*,3*R*)-(1*Z*)-Norchrysanthemic acid, a highly potent ingredient of synthetic pyrethroid containing a cyclopropane structure, was synthesized from readily available (*S*)-epoxide derived from 3-methyl-but-2-en-1-ol in 7 steps in 23% overall yield and with >98% ee. This sequence involves a *trans*-selective cyclopropane formation using the nitrile α-anion of (*S*)-3-mesyloxynitrile as the key step. The present chiral synthesis was performed with effective stereocontrol of both the chirality in the 1,3-positions on the cyclopropane and the *Z*-geometry of the propenyl group.
(ii) (+)-Grandisol, an insect sex pheromone possessing a characteristic cyclobutane structure, was synthesized from commercially available cyclopropyl methyl ketone (route A) or from commercially available 3-cyanopropylzinc bromide and 1-bromo-1-methylpropene (route B) in 10 or 8 steps in 6% or 8% overall yield and with 80% ee. This sequence involves a Shi asymmetric epoxidation of a trisubstituted olefin and a straightforward Stork-type asymmetric cyclobutane formation with clean S_N2 stereoinversion using the nitrile α-anion of the chiral epoxynitrile. The present expedient method is the second asymmetric total synthesis starting from achiral compounds.

Introduction

Carbanions at the α-position of nitriles (nitrile α-anions) serve as useful C-C bond-forming tools in organic syntheses.[1] Due to the feasible generation of these species using strong bases (LDA, MHMDS, NaH, etc.), alkylation and addition reactions using nitrile α-anions with their corresponding electrophiles are well-recognized methodology. Thorpe-Ziegler condensation between nitriles [2] and conjugate addition of cyanohydrin ether anions with enones as an umpolung methodology[3] are representative reactions. Notable studies of the utilization of nitrile anions are documented with regard to the stereoselective C-C bond-forming reactions.[4]

Compared with the privileged carbanion chemistry at the α-position of carbonyl compounds (aldehydes, ketones, esters, amides, and their derivatives) (pKa = ca. 19~30), however, less attention has been focused on nitrile α-anions (pKa = ca. 31~32). Moreover, limited effort has been invested in an enantioselective version with nitrile α-anions.[5] Our object in this report is a couple of chiral syntheses of small cycloalkanes utilizing characteristic properties of nitrile α-anions as the key strategy.

Chiral chrysanthemic acid (**1a**)[6] and grandisol (**2**)[7] are well-recognized natural products with the smallest three- and four-membered ring carbocycles, respectively, highlighted in organic chemistry textbooks and encyclopedias (Figure 1).[8] **1a** is the primary acid ingredient of natural pyrethroid insecticides and (+)-**2** is an insect sex pheromone of the cotton boll weevil.

Norchrysanthemic acid (**1b**) (R=H) is a potential acid component in metofluthrin,[9] which was recently developed as a distinctive synthetic analogue of **1a**. We first focused our attention on a chiral synthesis of **1b**, aimed at process chemistry, which is closely connected with our longstanding interests in synthetic chemistry for cyclopropane transformations[10] and related studies of novel chiral pyrethroids.[11] Next, we envisaged a concise asymmetric total synthesis of (+)-grandisol. Both chiral syntheses involve a common strategy, i.e. a clean intramolecular S_N2 ring-closings (**A** and **B**) based on the distinctive properties of compact and linear nitrile α-anions (Scheme 1).

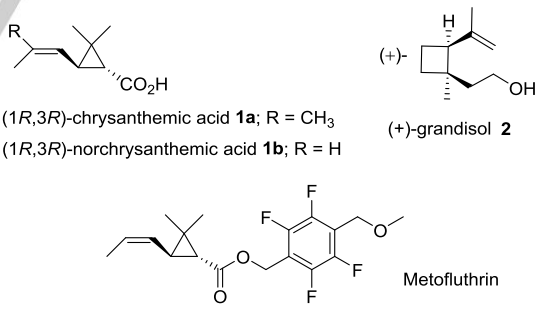

Figure 1. Representative examples of cyclopropane and cyclobutane.

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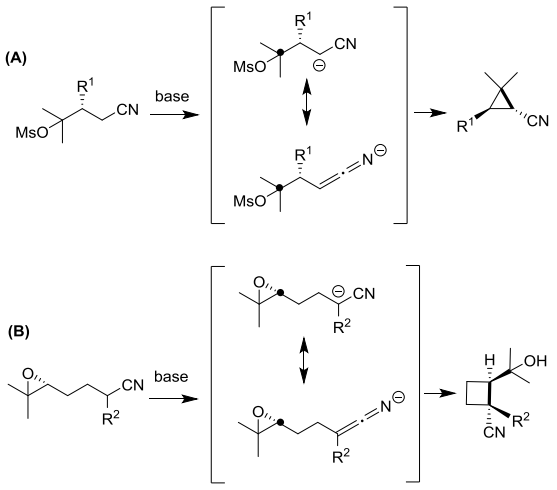


Scheme 1. Nitrile α-anion ring-closing strategy for chiral syntheses (**A**) and (**B**).

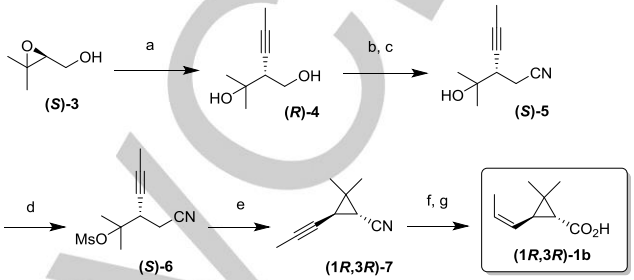
Results and Discussion

Despite both academic and industrial demands for the synthesis of norchrysanthemic acid (**1b**), only two methods have been reported to date. (i) (+)-3-Carene, a natural chiral pool compound, was transformed to **1b** in ca. 10% overall yield with *Z*:*E* = 90:10 in 8 steps.[9a,d,e] This method requires two ozonolysis steps and Wittig reaction, both of which are quite undesirable for the process production. (ii) Racemic chrysanthemic acid [(±)-**1a**] was converted to (±)-**1b** in ca. 15% overall yield with *Z*:*E* = 96:4 in 3 steps.[9f] This short-step method employed TBHP/catalytic SeO_2–oxidation in ionic liquid and decarboxylation using Cu_2O/quinoline reagent. The method provided racemic compound (±)-**1b** with steps that would be challenging to implement in an industrial setting.

Our chiral synthetic route to **1b** is depicted in Scheme 1. Readily available epoxy alcohol (*S*)-**3** (>98% ee), which was derived from prenyl alcohol by the standard Sharpless asymmetric epoxidation,[12] was treated with more than two equivalents of LiC≡CH. The desired clean SN2 epoxy-ring-opening proceeded regioselectively to give diol (*R*)-**4** in 96% yield. Notably, the plausible but undesirable Payne rearrangement of (*S*)-**3b** was completely circumvented during the reaction.[13] Selective monotosylation of primary alcohol in (*R*)-**4** using TsCl/Et_3N/cat. *N*-methylimidazole reagent,[14] and successive cyanation (KCN/cat. TBAB) gave nitrile (*S*)-**5**. Powerful mesylation (MsCl/Et_3N/*N*-methylimidazole)[15] of the tertiary alcohol (*S*)-**5** afforded cyanated mesylate precursor (*S*)-**6**.

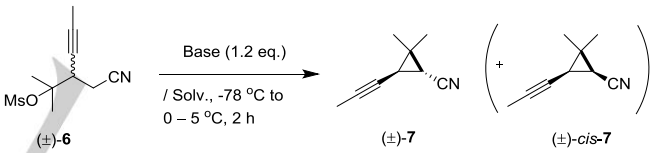
The key *trans*-selective ring-construction was examined using (±)-**6** (Table 1). Among several metal amide base and ether solvent systems screened, NaHMDS/CPME (cyclopentyl methyl ether)-THF (2:1) afforded the best results, producing cyclopropane **7** in 66% yield (*cis*/*trans* = 20 : 80) from (*S*)-**5** (entry 6). This conditions was adopted for chiral precursor (*S*)-**6**. This *trans*-selectivity is probably accounted for the thermodynamic stability.

Conversion of nitrile in chiral cyclopropane (1*R*,3*R*)-**7** to carboxylic group, followed by careful Lindlar reduction within 20 min produced the desired chiral norchrysanthemic acid **[**(1*R*,3*R*)-**1b]** in an overall 70% yield with nearly perfect *Z*-selectivity.[15] The present chiral synthesis of **1b** was performed in 23% overall yield and with >98% ee through 7 steps with effective stereocontrol both of chirality in 1,3-positions on the cyclopropane and of *Z*-geometry of propenyl group.



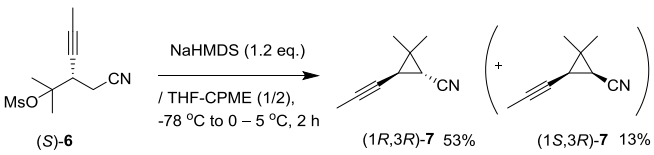
Scheme 2. Chiral synthesis of norchrysanthemic acid (**1b**). [a] Propyne (7.0 eq.), *n*BuLi (3.5 equiv) / THF, –78 °C to 20 °C, 14 h, 96%; [b] TsCl (1.5 eq.), Et_3N (1.5 eq.), *N*-methylimidazole (0.2 equiv) / toluene, 20 °C, 1 h; [c] KCN (3.0 equiv), TBAB (0.1 equiv) / DMSO, 60 °C, 14 h, 77% in 2 steps; [d] MsCl (1.5 equiv), Et_3N (1.5 equiv), *N*-methylimidazole (1.5 equiv) / toluene, 20 °C, 1.5 h; [e] NaHMDS (1.2 equiv) / THF–CPME (1:2), –78 °C to 0 °C, 2 h, 53% in 2 steps with *cis*-**7** (13%); [f] KOH (4.0 equiv) / ethylene glycol, reflux, 14 h, 79%; [g] H_2, Pd/$BaSO_4$ (1.2 equiv), quinolone (6.0 equiv) / hexane, 20 °C, 20 min, 89%.

Table 1. Cyclopropane formation of nitrile α-anion of (±)-**6**.



Entry	Base	Solvent	Yield / %[a]	*cis* / *trans*[b]
1	LDA	THF	24	45 : 55
2	LiHMDS	THF	22	42 : 58
3	NaHMDS	THF	30	47 : 53
4		(2-Me)THF	32	24 : 76
5		CPME[c]	46	26 : 74
6		THF/CPME[c] (1 / 2)	66	20 : 80

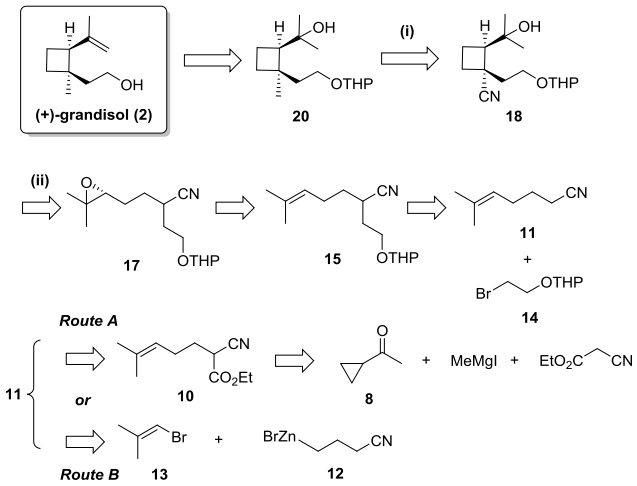
[a] From diol (±)-**5**. [b] Determined by ^1H NMR of the crude product. [c] cyclopentyl methyl ether.



We next envisaged another elaborated strategy for clean S_N2 inversion of nitrile α-anions aimed at expeditious asymmetric total synthesis of (+)-grandisol **2**. Chiral synthesis of (+)-**2** has received considerable attention because of its simple but unique cyclobutane structure possessing condensed methyl, hydroxyethyl, and isopropenyl groups. A literature survey for the chiral total syntheses of (+)-**2** revealed 13 examples, categorized into (i) standard optical resolution and kinetic resolution

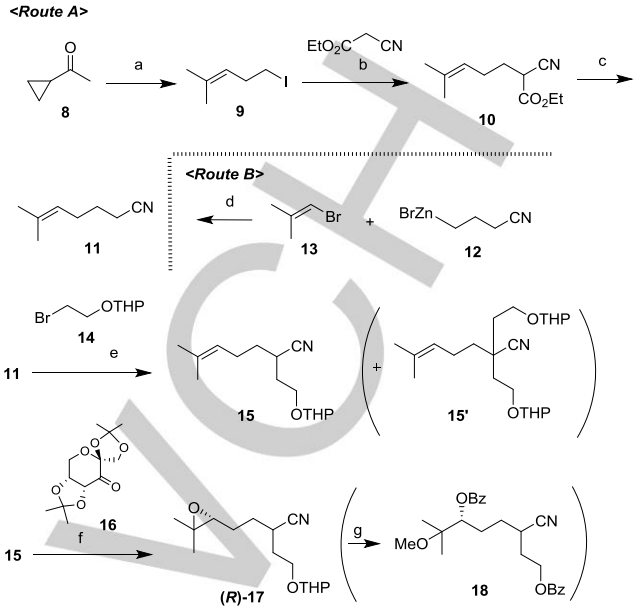
methods,[16-19] (ii) transformations of natural and unnatural chiral pools,[20-27] and (iii) utilization of catalytic asymmetric cycloaddition starting from achiral olefins.[28]

Our retrosynthetic strategy for (+)-**2** is illustrated in Scheme 3. The key feature involves (i) cyclobutane formation using chiral epoxide **17** by a revised Stork's racemic total synthesis of (±)-**2**,[29] (ii) Shi's asymmetric epoxidation of olefin intermediate **15**, and (iii) alternative syntheses of nitrile **11** (Routes A and B).



Scheme 3. Retrosynthetic pathway for grandisol (+)-(**2**).

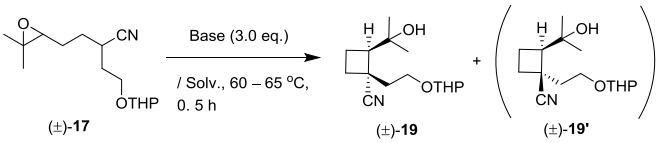
Scheme 4 depicts the synthetic route to the key chiral epoxide precursor **17**. Grignard reaction of MeMgI with commercially available cyclopropyl methyl ketone **8**, followed by treatment with H_2SO_4/H_2O gave homoallyl iodide **9** via a Juria-type cyclopropane-cleavage.[30] Alkylation of ethyl cyanoacetate with **9** and successive Krapcho decarboxylation[31] afforded olefinic nitrile **11**[32] in 67% overall yield (Route A). Notably, Negishi cross-coupling using commercially available Zn reagent **12** with vinyl bromide **13** directly produced **11** in 86% yield (Route B). Monoalkylation of **11** with THP-protected bromide **14** gave nitrile **15** with a small amount of dialkylated byproduct **15'**, which was easily removed by column chromatography. **15** was successfully converted to the chiral epoxide (*R*)-**17** by Shi's asymmetric epoxidation[33] using the mannitol-derived catalyst **16** in 96% yield with ca. 80% ee. To accurately determine the enantioselectivity, (*R*)-**17** was converted to benzoate derivative **18** in 2 steps. Fortuitously, this Shi's standard protocol matched for the desired "natural" grandisol (+)-**2** (vide infra).



Scheme 4. Synthesis of key chiral epoxide **17**. [a] MeMgI (1.1 eq.) / Et_2O, 0 °C, 1 h, 20 °C, 1 h. Work up with 30% H_2SO_4 aq., 84%; [b] DBU (2.0 eq.) / toluene, 80 °C, 1 h, 78%; [c] NaCl / DMSO, 150 °C, 4 h, 86%; [d] $Pd(PPh)_4$ (1 mol%) / THF, 50 °C, 3 h, 86%; [e] LDA (1.1 eq.) / THF-HPMA (5:1), –78 °C, 0.5 h, 20 °C, 14 h, 58% with **15'** (20%); [f] **16** (30 mol%), Oxone (1.38 eq.), K_2CO_3 (5.8 eq.), Bu_4NHSO_4 (4 mol%), / MeCN–DMM (1 / 2), 0 - 5 °C, 1.5 h, 96%; [g] cat. PPTS (0.1 eq.) / MeOH 20 °C, 1 h, PhCOCl, DMAP (0.1 eq.) / pyridine, 20 °C, 14 h, 47%.

The crucial cyclobutane formation using nitrile α-anion generated from (±)-**17** was investigated (Table 2). Among several base reagents and conditions screened, the reaction of (±)-**17** with LiHMDS at 60 °C in toluene solvent successfully afforded the desired cyclobutane (±)-**19** with its diastereomer (±)-**19'** in 83% yield (dr = ca. 6:4) (entry 1).[34,35] Slightly inferior results were obtained when using a TMEDA additive and using NaHMDS and KHMDS bases (entries 2, 4, 5).

Table 2. Cyclobutane formation of nitrile α-anion of (±)-**17**.



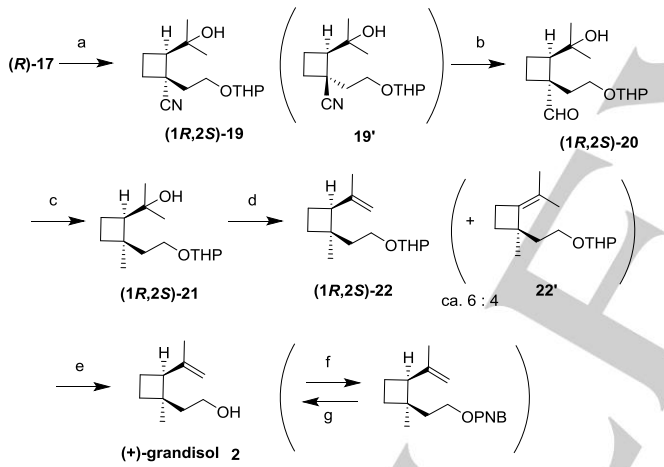
Entry	Base	Solvent	Yield / %[a]	(±)-**19** / (±)-**19'**
1	LiHMDS	toluene	83	60 : 40
2			65[b]	53 : 47
3		THF	72	51 : 49
4	NaHMDS	toluene	40	54 : 46
5	KHMDS		65	50 : 50

[a] Isolated yield. [b] 3.0 equiv of TMEDA was used.

The final stage of the asymmetric total synthesis of (+)-**2** is depicted in Scheme 5. Compared with the original Stork's approach[29] and Guerrero group's extensive studies[35] using racemic epoxynitrile substrates, the present designed route is more straightforward, because it eliminates oxidation of the secondary alcohol and Wittig olefination steps. In addition, Shi's

asymmetric epoxidation using tri-substituted olefins generally produces higher enantioselectivity than when using di-substituted olefins.[33] This background led us to use chiral epoxynitrile (*R*)-**17**.

Cyclobutane formation using (*R*)-**17** under the optimized conditions in Table 2 (entry 1) afforded the desired product (1*R*,2*S*)-**19** in a total yield of 83% with the diastereomer (1*R*,2*R*)-**19'**[36] with c.a. 6:4 ratio. DIBAL reduction of (1*R*,2*S*)-**19** gave aldehyde (1*R*,2*S*)-**20**, which was subjected to Wolff-Kishner reduction using H_2NNH_2/aqueous KOH to furnish cyclobutane (1*R*,2*S*)-**21** in 73% yield in 2 steps.[29,37] Dehydration of (1*R*,2*S*)-**21** using $SOCl_2$/pyridine afforded key precursor (1*R*,2*S*)-**22** with a minor byproduct 22' in a total yield of 75%. Deprotection of the THP group using Dowex 50Wx8[38] gave the desired crude (+)-grandisol **2**, which was purified by *p*-nitrobenzoylation and a deprotection sequence to remove alcohol derived from **22'**. Eventually, (+)-grandisol **2** was synthesized in 40% yield from (1*R*,2*S*)-**21** (80% ee based on the PNB ester). The present work is the second example of catalytic asymmetric synthesis in 10 steps (Route A) or 8 steps (Route B) in total 6% or 8% overall yield with 80% ee. Compared with the first method requiring 17 steps,[28] the present synthesis is expeditious.



Scheme 5. Asymmetric total synthesis of (+)-grandisol (**2**). [a] LiHMDS (3.0 eq.) / toluene, 60 °C, 0.5 h, 83%. dr = 6 : 4; [b] DIBAL (4.0 eq.) / toluene, 0 °C to 20 °C, 6 h; [c] H_2NNH_2 / H_2O (3.0 eq.), KOH (4.5 eq.) / diethyleneglycol 200 °C, 3 h, 73% in 2 steps; [d] $SOCl_2$ (1.2 eq.) / pyridine, 0 °C, 2 h, 75%; [e] Dowex 50Wx8 / MeOH, 20 °C, 14 h; [f] PNBCl (1.5 eq.), Py (2.0 eq.), DMAP (0.1 eq.) / CH_2Cl_2, 20 °C, 1 h. [g] LiOH (2.0 eq.) / THF–H_2O (1.5:1), 20 °C, 14 h.

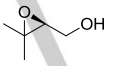
Conclusion

We achieved a couple of chiral syntheses of (1*R*,3*R*)-norchrysanthemic acid and an expedient asymmetric total synthesis of (+)-grandisol, both utilizing distinctive ring-closing methodologies with nitrile α-anions. The present small-ring formation involves different types of clean intramolecular S_N2 reactions. This protocol provides a new access for preparing a useful chiral cyclopropane and cyclobutane synthons.

Experimental Section

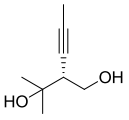
General Remarks: All reactions were carried out in oven-dried glassware under an argon atmosphere. Flash column chromatography was performed with silica gel Merck 60 (230-400 mesh ASTM). TLC analysis was performed on 0.25 mm Silicagel Merck 60 F_{254} plates. Melting points were determined on a hot stage microscope apparatus (AS ONE, ATM-01) and were uncorrected. NMR spectra were recorded on a JEOL DELTA 300 or JEOLRESONANCE ECX-500 spectrometer, operating at 300 MHz or 500 MHz for ^{1}H NMR and 75 MHz or 120 MHz for ^{13}C NMR. Chemical shifts (δ ppm) in $CDCl_3$ were reported downfield from TMS (= 0) for ^{1}H NMR. For ^{13}C NMR, chemical shifts were reported in the scale relative to $CDCl_3$ (77.00 ppm) as an internal reference. IR Spectra were recorded on a JASCO FT/IR-5300 spectrophotometer. Mass spectra were measured on a JEOL JMS-T100LC spectrometer. HPLC data were obtained on a SHIMADZU HPLC system (consisting of the following: SLC-10A, DGU-4A, LC-10AD, SIL-10A, CTO-10A and detector SPD-10AV measured at 254 nm) using DAISEL Chiracel OD-H column (25 cm) at 30 ˚C.

(*S*)-(3,3-dimethyloxiran-2-yl)methanol (2)



LiOH (1.33 g, 55.5 mmol) in H_2O (40 mL) was added to a stirred suspension of ester (**1**; >98% ee, 9.28 g, 37 mmol) in THF (55 mL) at 0 – 5 ºC under an Ar atmosphere, followed by being stirred at the same temperature for 0.5 h. The solution was diluted with Et_2O (90 mL) and CH_2Cl_2 (180 mL). Na_2SO_4 (45 g) was added to the stirred mixture, followed by being stirred at the same temperature for 20 min. The mixture was filtered and the filtrate was concentrated under reduced pressure. The obtained crude oil was purified by distillation to give the desired product (3.06 g, 81%).colorless oil; bp 175 – 180 ºC / 2.9 kPa. $[\alpha]_D^{25}$ –9.1 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.31 (s, 3H), 1.35 (s, 3H), 1.71 (br s, 1H), 2.99 (dd, *J* = 4.0 Hz, 6.9 Hz, 1H), 3.69 (dd, *J* = 6.9 Hz, *Jgem* = 12.0 Hz, 1H), 3.85 (dd, *J* = 4.0 Hz, *Jgem* = 12.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.8, 24.8, 58.9, 61.4, 63.8; IR (neat): ν_{max} = 3391, 2970, 2930, 1456, 1379, 1252, 1096, 1030, 856 cm^{-1}.

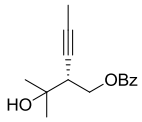
(*R*)-3-methyl-2-(prop-1-yn-1-yl)butane-1,3-diol (3)



*n*BuLi (1.63 M in hexane, 65.0 mL, 106 mmol) was added to a stirred solution of propyne (8.47 g, 211 mmol) in THF (80 mL) at -78 ºC under an Ar atmosphere, followed by being stirred at the same temperature for 0.5 h. (*S*)-epoxide (**2**; 3.08 g, 30.2 mmol) in THF (10 mL) was added slowly to the mixture at the same temperature, which was stirred for 0.5 h. The mixture was allowed to warm up to 20 – 25 ºC, and stirred for 14 h. The mixture was quenched with water, which was extracted three times with Et_2O (50 mL × 3). The combined organic phase was washed with brine, dried (Na_2SO_4) and concentrated. The obtained crude oil was purified by SiO_2-gel column chromatography (hexane-Et_2O = 3 : 1) to give the desired product (4.12 g, 96%).

pale yellow oil; $[\alpha]_D^{25}$ +9.2 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.33 (s, 6H), 1.76 (br s, 1H), 1.85 (d, *J* = 3.0 Hz, 3H), 1.94 (br s, 2H), 3.76–3.85 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 3.5, 26.5, 28.5, 45.5 63.3, 73.0, 76.7, 80.3; IR (neat): ν_{max} = 3333, 2972, 2922, 2886, 1377, 1364, 1173, 1148, 1063, 1028 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_8H_{14}O_2$ $[M + Na]^+$ 165.0891; found: 165.0896.

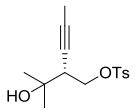
Determination of ee 3 by the derivatization to (*R*)-2-(2-hydroxypropan-2-yl)pent-3-yn-1-yl benzoate



PhCOCl (93 mg, 0.66 mmol) was added to a stirred solution of (*R*)-1,3-diol (**3**; 63 mg, 0.44 mmol), pyridine (70 mg, 0.88 mmol), DMAP (5 mg, 0.044mmol) in CH_2Cl_2 (1.0 mL) at 0 – 5 ºC under an Ar atmosphere, followed by being stirred at 20 – 25 ºC for 1 h. The mixture was quenched with water, which was extracted twice with CH_2Cl_2. The combined organic phase was washed with sat. $NaHCO_3$ aq., water, brine, dried (Na_2SO_4) and concentrated. The obtained crude oil was was purified by SiO_2-gel column chromatography (hexane-AcOEt = 15 : 1 – 10 : 1) to give the desired benzoate (87 mg, 80%).

colorless oil; $[\alpha]_D^{25}$ +70.9 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.36 (s, 3H), 1.37 (s, 3H), 1.83 (d, *J* = 2.3 Hz, 3H), 2.87–2.92 (m, 1H), 4.39 (dd, *J* = 7.8 Hz, *Jgem* = 10.8 Hz, 1H), 4.51 (dd, *J* = 6.0 Hz, *Jgem* = 10.8 Hz, 1H), 7.42–7.47 (m, 1H), 7.54–7.58 (m, 1H), 8.03–8.07 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 3.5, 27.2, 27.6, 44.0, 64.8, 71.5, 80.5, 128.4, 129.6, 130.1, 133.0, 166.4; IR (neat): ν_{max} = 3485, 3067, 2974, 2920, 1717, 1450, 1377, 1273, 1129, 708 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{15}H_{18}O_3$ [*M* + Na]$^+$ 269.1152; found: 269.1154. >99% ee; HPLC analysis (AD-H, flow rate 1.00 ml/min, solvent: hexane/2-propanol = 20/1) t_R(racemic) = 14.42 min and 16.60 min. t_R[(*R*)-form] = 16.82 min.

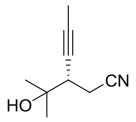
(*R*)-2-(2-hydroxypropan-2-yl)pent-3-yn-1-yl 4-methylbenzenesulfonate (4)



A solution of TsCl (6.45 g, 33.9 mmol) in toluene (10 mL) was added to a stirred solution of (*R*)-1,3-diol (**3**; 3.22 g, 22.6 mmol), *N*-methylimidazole (371 mg, 4.52 mmol), and Et_3N (3.43 g, 33.9 mmol) in toluene (55 mL) at 20 – 25 ºC under an Ar atmosphere, followed by being stirred at the same temperature for 1 h. The mixture was quenched with water, which was extracted twice with AcOEt. The combined organic phase was washed with water, brine, dried (Na_2SO_4) and concentrated. The obtained crude oil was purified by SiO_2-gel column chromatography (hexane-AcOEt = 15 : 1 - 3 :1) to give the desired product (6.43 g, 96%).

white crystals; mp 78 – 80 ºC. $[\alpha]_D^{25}$ +21.8 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.24 (s, 3H), 1.26 (s, 3H), 1.64 (br s, 1H), 1.77 (d, *J* = 2.3 Hz, 3H), 2.46 (s, 3H), 2.69–2.74 (m, 1H), 4.06 (dd, *J* = 7.8 Hz, *Jgem* = 9.6 Hz, 1H), 4.23 (dd, *J* = 6.0 Hz, *Jgem* = 9.6 Hz, 1H), 7.33–7.37 (m, 2H), 7.79–7.83 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 3.5, 21.6, 27.3, 27.4, 44.0, 69.8, 71.3, 75.4, 76.7, 80.9, 128.0, 129.8, 132.9, 144.9; IR (neat): ν_{max} = 3543, 2984, 2926, 1597, 1331, 1169, 1119, 1096, 951, 816 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{15}H_{20}O_4S$ [*M* + Na]$^+$ 319.0980; found: 319.0984.

(*S*)-3-(2-Hydroxypropan-2-yl)hex-4-ynenitrile (5)

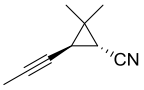


A solution of (*R*)-*p*-toluenesulfonate (**4**; 3.49 g, 11.8 mmol) in DMSO (10 mL) was added to stirred suspension of KCN (2.30 g, 35.4 mmol) and Bu_4NBr (TBAB, 380 mg, 1.2 mmol) in DMSO (25 mL) at 20 – 25 ºC under an Ar atmosphere, followed by being stirred at 60 – 65 ºC for 14 h. The mixture was quenched with sat. $NaHCO_3$ aq., which was extracted twice with Et_2O. The combined organic phase was washed with water, brine, dried (Na_2SO_4) and concentrated. The obtained crude oil was purified by SiO_2-gelcolumn chromatography (hexane-AcOEt = 9 : 1) to give the desired product (1.43 g, 80%) and 2-methyl-3-methylenehex-4-yn-2-ol as a by-product (147 mg, 10%).

5 : pale yellow oil; $[\alpha]_D^{25}$ +89.7 (*c*, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.32 (s, 6H), 1.62 (br s, 1H), 1.87 (d, *J* = 2.3 Hz, 3H), 2.48–2.57 (m, 1H), 2.66–2.76 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 3.5, 19.2, 26.4, 27.5, 41.3, 71.6, 76.1, 81.6, 118.9; IR (neat): ν_{max} = 3460, 2976, 2922, 2855, 2253, 1732, 1377, 1261, 1148 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_9H_{13}NO$ [*M* + Na]$^+$ 174.0896; found: 174.0895.

By-product: colorless oil; ^{1}H NMR (400 MHz; $CDCl_3$): δ = 1.42 (s, 6H), 1.69 (br s, 1H), 1.98 (s, 3H), 5.31 (s, 1H), 5.46 (s, 1H).

(1*R*,3*R*)-2,2-dimethyl-3-(prop-1-yn-1-yl)cyclopropane-1-carbonitrile (7)



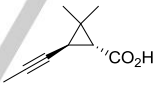
A solution of MsCl (2.00 g, 17.4 mmol) in toluene (10 mL) was added to a stirred suspension of (*S*)-nitrile (**5**; 1.76 g, 11.6 mmol), *N*-methylimidazole (1.43 g, 17.4 mmol), and Et_3N (1.77 mg, 17.4 mmol) in toluene (25 mL) at 20 – 25 ºC under an Ar atmosphere, followed by being stirred for at the same temperature for 1.5 h. The mixture was quenched with 1M-HCl aqueous solution, which was extracted twice with AcOEt. The combined organic phase was washed with brine, dried (Na_2SO_4) and concentrated. The obtained crude mesylate (**6**; 2.40 g) was used for the next step without purification.

Mesylate (**6**; 2.40 g) in CPME/THF (2 : 1, 10 mL) was added to a stirred solution of NaHMDS (0.6 M in toluene, 21 mL, 12.6 mmol) in CPME/THF (2 : 1, 96 mL) at –78 ºC under an Ar atmosphere, followed by being stirred at the same temperature for 0.5 h. The mixture was allowed to warm to 0 – 5 ºC, and was stirred for 2 h. The mixture was reversely quenched with water, which was extracted twice with Et_2O. The combined organic phase was washed with brine, dried (Na_2SO_4) and concentrated. The obtained crude oil was purified by SiO_2-gelcolumn chromatography (hexane-Et_2O = 100 : 1) to give the desired product (812 mg, 53% for 2 steps).

***trans*-7**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.68 (s, 3H), 1.82 (s, 3H), 1.85 (d, *J* = 2.3 Hz, 3H), 2.59 (dd, *J* = 8.2 Hz, *Jgem* = 16.5 Hz, 1H), 2.75 (dd, *J* = 5.0 Hz, *Jgem* = 16.5 Hz, 1H), 3.05 (s, 3H), 3.16–3.21 (m, 1H).

***cis*-7**: pale yellow oil; $[\alpha]_D^{25}$ +180.2 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.26 (s, 3H), 1.29 (d, *J* = 5.2 Hz, 1H), 1.32 (s, 3H), 1.71–1.73 (m, 1H), 1.80 (d, *J* = 2.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 3.5, 18.4, 20.9, 22.3, 23.3, 26.0, 74.8, 77.5, 119.1; IR (neat): ν_{max} = 2963, 2922, 2234, 1454, 1381, 1269, 1119, 1053, 1028 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_9H_{11}N$ [*M* + Na]$^+$ 156.0789; found: 156.0786.

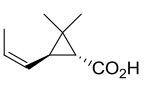
(1*R*,3*R*)-2,2-dimethyl-3-(prop-1-yn-1-yl)cyclopropane-1-carboxylic acid (8)[15]



A suspension of (1*R*,3*R*)-nitrile (**7**; 212 mg, 1.59 mmol) and KOH (256 mg, 6.36 mmol) in ethyleneglycol (3.0 mL), which was stirred at reflux for 14 h. The mixture was cooled to 20 – 25 ºC and was extracted twice with Et_2O. Separated ethyleneglycol layer was acidified using 1M-HCl aq. solution, which was re-extracted twice with Et_2O. The combined organic phase was washed with water, brine, dried (Na_2SO_4) and concentrated. The obtained crude oil was purified by SiO_2-gelcolumn chromatography (hexane-Et_2O = 10 : 1 – 5 : 1) to give the desired product (190 mg, 79%).

white crystal; mp 108 – 110 ºC; $[\alpha]_D^{25}$ +93.0 (*c*, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.25 (s, 3H), 1.29 (s, 3H), 1.62 (d, *J* = 5.0 Hz, 1H), 1.80 (d, *J* = 1.8 Hz, 3H), 1.91–1.93 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 3.5, 19.1, 23.0, 23.6, 29.7, 34.6, 76.1, 76.4, 177.5; IR (neat): ν_{max} = 2961, 2922, 2610, 1682, 1443, 1333, 1288, 1244, 1202, 1111, 947 cm^{-1}.

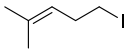
(1*R*,3*R*)-2,2-dimethyl-3-((*Z*)-prop-1-enyl)cyclopropanecarboxylic acid (1b)[15]



A suspension of (1*R*,3*R*)-carboxylic acid (**8**; 23 mg, 0.15 mmol), 5% Pd-$BaSO_4$ (16 mg, 7.5 μmol), and quinoline (116 mg, 0.09 mmol) in hexane (1.5 ml), equipped with a H_2 balloon, was stirred stirred at 20 – 25 ºC for 20 min. The mixture was filtered through Celite® (No.503) with glass filter washing by Et_2O, and the filtrate was concentrated under reduced pressure. The residue was diluted with Et_2O, which was washed with 1M-NaOH aq. solution and the separated aqueous phase was acidified using 1M-HCl aq. solution. The obatained mixture was re-extracted twice with Et_2O. The combined organic phase was washed

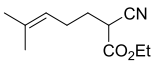
with water, brine, dried (Na_2SO_4) and concentrated. The obtained crude oil was purified by SiO_2-gelcolumn chromatography (hexane-Et_2O = 40 : 1) to give the desired product (21 mg, 89%).
pale yellow oil; $[\alpha]_D^{25}$ +8.3 (*c*, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.17 (s, 3H), 1.25 (br s, 1H), 1.32 (s, 3H), 1.47 (d, 1H, *J* = 5.5 Hz), 1.71 (dd, *J* = 1.4 Hz, *Jgem* = 6.9 Hz, 3H), 2.20 (dd, *J* = 5.5 Hz, *Jgem* = 7.8 Hz, 1H), 5.10–5.17 (m, 1H), 5.57–5.65 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.4, 20.4, 22.2, 29.8, 32.5, 34.6, 126.7, 127.4, 178.3; IR (neat): ν_{max} = 3024, 2924, 1688, 1449, 1416 cm^{-1}.

5-Iodo-2-methylpent-2-ene (9)[39]



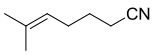
Following the reported procedure[39]; MeI (15.0 mL, 0.24 mol) in Et_2O (100 mL) was added to a stirred suspension of granular Mg (5.84 g, 0.24 mol) and cat. I_2 at 20 – 25 ºC under an Ar atmosphere, and the mixture was stirred at 20–25 °C for 0.5 h. After cooling down to 0 – 5 °C, cyclopropyl methyl ketone (16.8 g, 0.20 mol) in THF (100 mL) was added to the mixture at the same temperature. After stirring at 20 – 25°C for 1 h, the mixture was poured into ice-cooled 30% H_2SO_4 aq. (100 mL) with vigourously stiiring for 1 h. The resulting mixture was extracted twice with Et_2O and combined organic phase was washed with water, brine, dried (Na_2SO_4) and concentrated. The obtained crude oil was purified by distillation to give the desired product **9** (35.3 g, 84%).
purple coloured oil; bp 50 – 52 ºC / 3.0 kPa; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.62 (s, 3H), 1.70 (s, 3H), 2.57 (q, *J* = 7.5 Hz, 14.9 Hz, 2H), 3.11 (t, *J* = 7.5 Hz, 2H), 5.07–5.12 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 6.0, 17.9, 25.6, 32.4, 123.0, 134.3; IR (neat): ν_{max} = 2967, 2913, 1423, 1375, 1248, 1209, 1165, 982, 831 cm^{-1}.

Ethyl 2-cyano-6-methylhept-5-enoate (10)



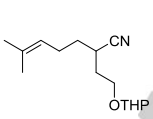
Ethyl cyanoacetate (37.3 g, 0.33 mol) in toluene (80 mL) and iodide **9** (34.6 g, 165 mmol) in toluene (80 mL) were successively added to a stirred solution of DBU (50.2 g, 0.33 mol) in toluene (165 mL) at 0 – 5 ºC under an Ar atmosphere, followed by being stirred at 80 - 85 °C for 1 h. The resulting mixture was quenched with water, which was extracted twice with Et_2O. The combined organic phase was washed with 1M-HCl aq., brine, dried (Na_2SO_4), and concentrated. The obtained crude oil was purified by SiO_2–column chromatography (hexane/AcOEt = 20 : 1) to give the desired product **10** (25.1 g, 84%).
colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.33 (t, 3H, *J* = 6.9 Hz), 1.64 (s, 3H), 1.71 (s, 3H), 1.99 (q, *J* = 7.5 Hz, 14.9 Hz, 2H), 2.22 (q, *J* = 7.5 Hz, 14.9 Hz, 2H), 3.49 (t, *J* = 6.9 Hz, 1H), 4.26 (q, *J* = 6.9 Hz, 14.3 Hz, 2H), 5.03–5.08 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.0, 17.7, 25.1, 25.7, 29.9, 36.8, 62.7, 116.6, 121.1, 134.8, 166.3; IR (neat): ν_{max} = 2933, 1742, 1447, 1369, 1254, 1192, 1109, 1022, 854 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{11}H_{17}NO_2$ [*M* + Na]$^+$ 218.1157; found: 218.1167.

6-Methylhept-5-enenitrile (11)[32]

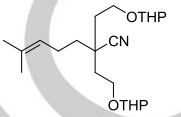


(i) Krapco decarboxylation method; A suspension of nitrile **10** (30.0 g, 154 mmol), NaCl (27.0 g, 0.46 mol), and water (8.33 g, 0.46 mol) in DMSO (300 mL) was stirred stirred at 150 – 155 ºC for 4 h. The resulting mixture was quenched with water, which was extracted twice with Et_2O. The combined organic phase was washed with a large amounts of water to remove DMSO, brine, dried (Na_2SO_4) and concentrated. The obtained crude oil was purified by distillation to give the desired product **11** (16.4 g, 86%).
(ii) Negishi cross-coupling method; 3-Cyanopropylzinc bromide (**12**; 0.5 M solution in THF, 5.6 mL, 2.8 mmol, commercially available) was added to a stirred suspension of 1-bromo-2-methylprop-1-ene (**13**; 276 mg, 2.0 mmol) and $Pd(PPh_3)_4$ (23 mg, 20 µmol) in THF (4.0 mL) at 20 – 25 ºC under an Ar atmosphere, and the mixture was stirred at 50 – 55 °C for 3 h. The resulting mixture was quenched with 1M-HCl aq., which was extracted twice with Et_2O. The combined organic phase was washed with water, brine, dried (Na_2SO_4) and concentrated. The obtained crude oil was purified by SiO_2–column chromatography (hexane/Et_2O = 20 : 1) to give the desired product **11** (212 mg, 86%).
colorless oil; bp 85 – 92 ºC / 3.4 kPa; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.63 (s, 3H), 1.71 (s, 3H), 1.67–1.73 (m, 2H), 2.15 (q, *J* = 7.5 Hz, 14.3 Hz, 2H), 2.32 (t, *J* = 7.5 Hz, 2H), 5.01 (t, *J* = 7.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 16.4, 17.8, 25.5, 25.7, 26.8, 119.9, 121.8, 134.1; IR (neat): ν_{max} = 2932, 2247, 1674, 1450, 1377, 1225, 1109, 986, 853, 731 cm^{-1}.

6-Methyl-2-[2-((tetrahydro-2*H*-pyran-2-yl)oxy)ethyl]hept-5-enenitrile (15)



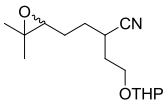
15



15'

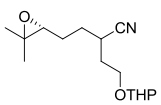
*n*BuLi (1.63 M in hexane, 88 mL, 143 mmol) was added to stirred solution of *i*Pr_2NH (14.5 g, 143 mmol) in THF/HMPA (5:1, 168 mL) at 0 – 5 ºC under an Ar atmosphere, followed by being stirred for 15 min. The mixture was cooled down to −78 °C and nitrile **11** (16.0 g, 130 mmol) in THF/HMPA (5:1, 30 mL) was added to the mixture at the same temperature. After stirring for 0.5 h, 2-bromoethanol tetrahydropyranyl ether (**14**; 32.6 g, 156 mmol) in THF/HMPA (5:1, 30 mL) was added to the mixture. The mixture was stirred at the same temperature for 0.5 h and was allowed to warm up to 20 – 25 °C, followed by being stirred for 14 h. The mixtre was poured onto ice-cooled sat. NH_4Cl aq. solution, which was extracted twice with Et_2O. The combined organic phase was washed with a large amounts of water to remove HMPA, brine, dried (Na_2SO_4), and concentrated. The obtained crude oil was purified by SiO_2–column chromatography (hexane-AcOEt = 20 : 1) to give the desired product **15** (19.0 g, 58%) with dialkylated byproduct **15'** (9.9 g, 20%).
15: colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.49–1.90 (m, 10H), 1.64 (s, 3H), 1.70 (s, 3H), 2.14–2.25 (m, 2H), 2.77–2.85 (m, 1H), 3.49–3.57 (m, 2H), 3.82–3.94 (m, 2H), 4.58–4.62 (m, 1H), 5.07 (t, *J* = 7.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 17.8, 19.3, 19.6, 25.4, 25.55, 25.58, 25.7, 27.9, 28.0, 30.5, 30.6, 32.3, 32.4, 62.1, 62.6, 64.1, 64.4, 98.6, 99.4, 122.0, 122.2, 133.57, 133.62; IR (neat): ν_{max} = 2938, 2868, 2237, 1738, 1454, 1377, 1354, 1136, 1123, 1034, 980 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{15}H_{25}NO_2$ [*M* + Na]$^+$ 274.1783; found: 274.1786.
15' : ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.50–1.85 (m, 18H), 1.63 (s, 3H), 1.69 (s, 3H), 1.92–2.01 (m, 4H), 2.15 (q, *J* = 7.5 Hz, 16.6 Hz, 2H), 3.50–3.60 (m, 4H), 3.80–3.99 (m, 4H), 4.60 (t, *J* = 3.4 Hz, 2H), 5.07 (t, *J* = 7.5 Hz, 1H).

4-(3,3-Dimethyloxiran-2-yl)-2-[2-((tetrahydro-2*H*-pyran-2-yl)oxy)ethyl]butanenitrile [(±)-17]



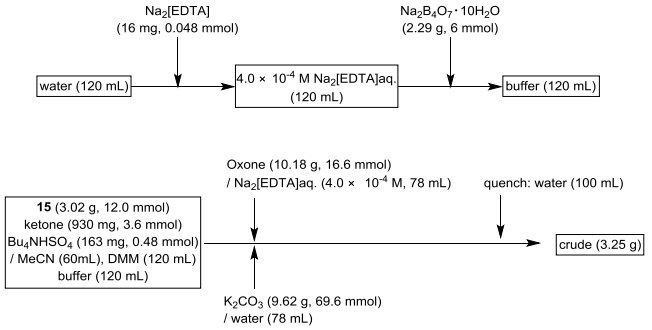
*m*CPBA (4.66 g, 27 mmol) in CH_2Cl_2 (30 mL) was added to a stirred solution of nitrile **15** (3.77 g, 15 mmol) in CH_2Cl_2 (15 mL) at 0 – 5 ºC under an Ar atmosphere, and the mixture was stirred at 20 – 25 ºC for 14 h. The mixture was quenched with water, which was extracted twice with CH_2Cl_2. The combined organic phase was washed with sat. $NaHCO_3$ aq., brine, dried (Na_2SO_4) and concentrated. The obtained crude oil was purified by SiO_2–column chromatography (hexane/AcOEt = 8:1 – 2:1) to give the desired product (±)-**17** (3.85 g, 96%).
colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.30 (s, 3H), 1.33 (s, 3H), 1.50–1.63 (m, 5H), 1.68–1.93 (m, 7H), 2.72–2.75 (m, 1H), 2.84–2.94 (m, 1H), 3.50–3.57 (m, 2H), 3.82–3.95 (m, 2H), 4.58–4.62 (m, 1H).

4-[(*R*)-3,3-Dimethyloxiran-2-yl]-2-[2-((tetrahydro-2*H*-pyran-2-yl)oxy)ethyl]butanenitrile (17)



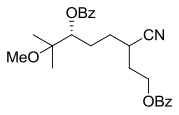
Oxone® (10.18 g, 16.6 mmol) in Na_2[EDTA] aq. (4.0 × 10^{-4} M, 78 mL) and K_2CO_3 (9.62 g, 69.6 mmol) in water (78 mL) were simultaneously and proportionally added dropwise to a stirred suspension of nitrile **15** (3.02 g, 12.0 mmol),

mannitol–derived ketone **16** (930 mg, 3.6 mmol), and Bu_4NHSO_4 (163 mg, 0.48 mmol) in MeCN (60 mL), dimethoxymethane (120 mL) and buffer (0.05 M solution of $Na_2B_4O_7 \cdot 10H_2O$ in 4.0×10^{-4} M Na_2[EDTA] aq., 120 mL) at 0 – 5 ºC over a period of 1.5 h under an Ar atmosphere. The resulting mixture was quenched with water, which was extracted twice with AcOEt. The combined organic phase was washed with water, brine, dried (Na_2SO_4) and concentrated. The obtained crude oil was purified by SiO_2–column chromatography (hexane/AcOEt = 8:1 – 2:1) to give the desired product **17** (3.08 g, 96%; c.a. 80% ee determined by derivative **18**).



colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.30 (s, 3H), 1.33 (s, 3H), 1.50–1.63 (m, 5H), 1.68–1.93 (m, 7H), 2.72–2.75 (m, 1H), 2.84–2.94 (m, 1H), 3.50–3.57 (m, 2H), 3.82–3.95 (m, 2H), 4.58–4.62 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 18.70, 18.75, 19.30, 19.34, 19.61, 19.65, 24.7, 25.3, 26.1, 26.2, 26.8, 28.1, 28.2, 28.65, 28.73, 28.9, 29.0, 29.5, 29.6, 30.45, 30.53, 32.3, 32.4, 32.6, 32.7, 58.3, 58.5, 62.1, 62.2, 62.6, 62.7, 63.0, 63.4, 63.5, 63.9, 64.0, 64.3, 98.6, 98.7, 99.41, 99.43, 121.5, 121.6; IR (neat): ν_{max} = 2941, 2237, 1454, 1200, 1123, 1076, 1033, 978, 870, 813 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{15}H_{25}NO_3$ [*M* + Na]$^+$ 290.1732; found: 290.1732.

(6*R*)-3-Cyano-7-methoxy-7-methyloctane-1,6-diyl dibenzoate (18)

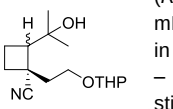


A suspension of (*R*)–epoxynitrile **17** (134 mg, 0.50 mmol) and PPTS (13 mg, 50 µmol) in MeOH (1.0 mL) was stirred at 20 – 25^{o}C for 14 h. The mixture was quenched with water, which was extracted twice with AcOEt. The combined organic phase was washed with water, brine, dried (Na_2SO_4) and concentrated. The obtained crude oil product (115 mg) was used for the next step without purification.

PhCOCl (211 mg, 1.5 mmol) was added to a stirred solution of the above crude product **(**115 mg), pyridine (119 mg, 1.5 mmol), and DMAP (6 mg, 50 µmol) in CH_2Cl_2 (1.0 mL) at 0 – 5 ºC under an Ar atmosphere, followed by being stirred at 20 – 25 ºC for 14 h. The mixture was quenched with water, which was extracted twice with CH_2Cl_2. The combined organic phase was washed with sat. $NaHCO_3$ aq. and brine, dried (Na_2SO_4) and concentrated. The obtained crude oil was purified by SiO_2–gel column chromatography (hexane/AcOEt = 12:1 – 3:1) to give the desired dibenzoate **18** (100 mg, 47% in 2 steps, *dr* 53 : 47,)

colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.20 (s, 3H x 47/100), 1.21 (s, 3H x 53/100), 1.232 (s, 3H x 53/100), 1.238 (s, 3H x 47/100), 1.59–2.22 (m, 6H), 2.68–3.00 (m, 1H), 3.246 (s, 3H x 47/100), 3.254 (s, 3H x 53/100), 4.36–4.58 (m, 2H), 5.12–5.24 (m, 1H), 7.34–7.48 (m, 4H), 7.50–7.62 (m, 2H), 7.90–8.12 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 20.5, 20.6, 22.3, 27.0, 27.1, 28.5, 28.85, 28.91, 29.2, 31.5, 31.8, 49.8, 61.9, 76.1, 76.2, 76.9, 77.6, 121.07, 121,10, 128.4, 128.5, 129.7, 129.8, 133.1, 133.2, 166.20, 166.23, 166.3; HRMS (ESI): *m/z* calcd for $C_{25}H_{29}NO_5$ [*M* + Na]$^+$ 446.1943; found: 446.1949; 81% ee; HPLC analysis (OD–H, flow rate 1.00 ml/min, solvent: hexane/2–propanol = 30/1) t_R(racemic) = 21.92 min and 23.46 min and 25.01 min. t_R[(6*R*)–form] = 23.80 min. t_R[(6*S*)–form] = 25.25 min.

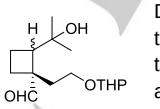
2-[(2*S*)-2-Isocyano-2-[2-((tetrahydro-2*H*-pyran-2-yl)oxy)ethyl)cyclobutyl]propan-2-ol (19), (19')



(*R*)–Epoxynitrile **17** (3.58 g, 13.4 mmol) in toluene (30 mL) was added to a stirred solution of LiHMDS (1.0 M in toluene, 40 mL, 40.2 mmol) in toluene (240 mL) at 20 – 25 ºC under an Ar atmosphere, and the mixture was stirred at 60 – 65 ^{o}C for 0.5 h. After cooling down to 0 – 5 ^{o}C, the mixture was quenched with 0.5 M–HCl aq. solution and was extracted twice with Et_2O. The combined organic phase was washed with water, brine, dried (Na_2SO_4) and concentrated. The obtained crude oil was purified by SiO_2–column chromatography (hexane–AcOEt = 20 : 1) to give the desired product **19** and **19'**(*dr* 60 : 40, 2.97 g, 83%).

pale yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.12 (s, 3H x 40/100), 1.13 (s, 3H x 60/100), 1.35 (s, 3H x 40/100), 1.36 (s, 3H x 60/100), 1.51–1.95 (m, 8H), 2.08–2.41 (m, 5H), 2.69–2.74 (m, 1H), 3.50 (m, 2H), 3.83–4.05 (m, 2H), 4.61–4.64 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 18.9, 19.0, 19.27, 19.32, 25.3, 25.4, 27.5, 28.6, 28.8, 28.9, 29.1, 30.4, 30.5, 30.6, 30.8, 36.36, 36.39, 52.8, 62.1, 62.2, 64.6, 64.5, 71.0, 71.1, 98.9, 99.0, 124.1, 124.2; HRMS (ESI): *m/z* calcd for $C_{15}H_{25}NO_3$ [*M* + Na]$^+$ 290.1732; found: 290.1726.

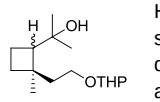
(1*S*)-2-(2-Hydroxypropan-2-yl)-1-[2-((tetrahydro-2*H*-pyran-2-yl)oxy)ethyl]cyclobutane-1-carbaldehyde (20)



DIBAL (1.0 M in toluene, 38 mL, 38 mmol) was added to a stirred solution of nitrile **1.2–7 (**2.53 g, 9.5 mmol) in toluene (28 mL) at 0 – 5 ºC under an Ar atmosphere, and the mixture was stirred for 6 h at 20 – 25^{o}C. The resulting mixture was quenched with sat. sodium potassium tartaric acid aq. solution (40 mL), which was extracted twice with AcOEt. The combined organic phase was washed with water, brine, dried (Na_2SO_4) and concentrated. The obtained product **20** (1.91 g) was used without purification for next steps.

colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.12 (s, 3H), 1.25 (s, 3H), 1.35–1.86 (m, 9H), 2.03–2.14 (m, 1H), 2.27–2.38 (m, 2H), 2.41–2.49 (m, 2H), 3.27–3.52 (m, 2H), 3.60–3.91 (m, 2H), 4.44 (s, 1H x 40/100), 4.58 (s, 1H x 60/100), 9.58 (s, 1H x 40/100), 9.61 (s, 1H x 60/100).

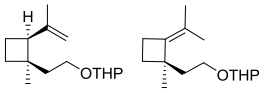
2-[(2*R*)-2-methyl-2-(2-((tetrahydro-2*H*-pyran-2-yl)oxy)ethyl)cyclobutyl]propan-2-ol (21)



$H_2NNH_2 \cdot H_2O$ (1.06 g, 21.3 mmol) was added to a stirred solution of aldehyde **20** (1.91 g) in diethyleneglycol (21 mL) at 20 – 25 ºC under an Ar atmosphere. After being stirred at 200 – 205 ^{o}C for 0.5 h, KOH (1.27 g, 32.0 mmol) in water (0.90 mL) was added to the mixture. The mixture was stirred at the same temperature for 3 h. After cooling down to 20 – 25 ^{o}C, the mixture was quenched with water, which was extracted twice with Et_2O. The combined organic phase was washed with water, brine, dried (Na_2SO_4) and concentrated. The obtained crude oil was purified by SiO_2–column chromatography (hexane/AcOEt = 8 : 1 – 5 : 1) to give the desired product **21** (*dr* 60 : 40, 1.47 g, 60% in 2 steps).

colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.09 (s, 3H), 1.13 (s, 3H x 40/100), 1.14 (s, 3H x 60/100), 1.23 (s, 3H x 40/100), 1.24 (s, 3H x 60/100), 1.51–2.18 (m, 14H), 3.34–3.55 (m, 2H), 3.74–3.90 (m, 2H), 4.57–4.60 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 17.8, 19.5, 19.7, 25.4, 28.2, 28.8, 28.9, 29.0, 29.1, 30.3, 30.58, 30.64, 30.7, 34.2, 41.7, 41.8, 56.1, 56.2, 62.2, 62.4, 64.8, 64.9, 71.9, 72.0, 98.9, 99.1; HRMS (ESI): *m/z* calcd for $C_{15}H_{28}O_3$ [*M* + Na]$^+$ 279.1936; found: 279.1939.

2-[2-((1*R*,2*S*)-1-Methyl-2-(prop-1-en-2-yl)cyclobutyl)ethoxy]tetrahydro-2*H*-pyran (22)[29,38]

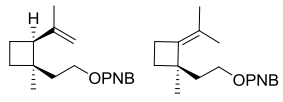


22 **22'**

$SOCl_2$ (293 mg, 2.5 mmol) was added to a stirred solution of alcohol **21** (548 mg, 2.1 mmol) in pyridine (4.1 mL) at 0 – 5 ºC under an Ar atmosphere, followed by being stirred for 2 h. The mixture was quenched with water, which was extracted twice with AcOEt. The combined organic phase was washed with 1M HCl aq. solution, water, brine, dried (Na_2SO_4) and concentrated. The obtained crude oil was purified by SiO_2–column chromatography (hexane/AcOEt = 5 : 1) to give the desired product **22** (383 mg, 75%).

colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.16 (s, 3H x 40/100), 1.18 (s, 3H x 60/100), 1.41–2.02 (m, 12H x 60/100 + 10 H x 40/100), 1.45 (s, 3H x 40/100), 1.67 (s, 3H), 2.39–2.45 (m, 2H x 40/100), 2.54 (t, *J* = 9.2 Hz, 1H x 60/100), 3.32–3.55 (m, 2H), 3.72–3.91 (m, 2H), 4.53–4.61 (m, 1H), 4.64 (s, 1H x 60/100), 4.83 (s, 1H x 60/100); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.6, 19.1, 19.3, 19.6, 23.2, 23.8, 25.4, 25.8, 26.0, 28.3, 28.4, 28.89, 28.94, 29.05, 29.12, 30.8, 33.3, 39.0, 41.2, 44.6, 52.5, 62.1, 62.26, 62.29, 64.5, 64.6, 65.1, 98.88, 98.92, 109.7, 122.4, 138.62, 138.65, 145.0, 145.1; HRMS (ESI): *m/z* calcd for $C_{15}H_{26}O_2$ $[M + Na]^+$ 261.1828; found: 261.1830.

2-[(1*R*,2*S*)-1-Methyl-2-(prop-1-en-2-yl)cyclobutyl]ethyl 4–nitrobenzoate (23)



23 **23'**

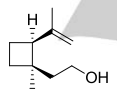
Dowex 50Wx8 (301 mg) was added to a stirred solution of mixture of THP ethers **22** and **23'** (429 mg, 4.2 mmol) in MeOH (28 mL) at 20 – 25 ºC under an Ar atmosphere, followed by being stirred at the same temperature for 14 h. The mixture was filtered through Celite® (No.503) and the filtrate was concentrated under reduced pressure. The obtained crude (+)–grandisol (**2**; 730 mg) was subjected to the following further purification.

4–Nitrobenzoyl chloride (1.31 g, 7.0 mmol) in CH_2Cl_2 (4.0 mL) was added to a stirred solution of crude (+)–grandisol (**2**; 30 mg, 4.7 mmol), pyridine (743 mg, 9.4 mmol), and DMAP (57 mg, 0.50 mmol) in CH_2Cl_2 (10 mL) at 20 – 25 ºC under an Ar atmospher, followed by being stirred for 2 h. The mixture was quenched with water, which was extracted twice with CH_2Cl_2. The combined organic phase was washed with 1M HCl aq. solution, water, brine, dried (Na_2SO_4) and concentrated. The obtained crude solid was purified by SiO_2–column chromatography (hexane/AcOEt = 300 : 1) to give the desired product **23** (521 mg, 41% in 2 steps) and the by–product **23'** (369 mg, 29% in 2 steps).

23: pale yellow crystals; mp 74 – 76 ºC; $[\alpha]_D^{25}$ −1.2 (*c* 0.5, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.26 (s, 3H), 1.59–1.78 (m, 2H), 1.70 (s, 3H), 1.83–1.89 (m, 1H), 1.94–2.03 (m, 2H), 2.62 (t, *J* = 9.2 Hz, 1H), 4.36–4.46 (m, 2H), 4.69 (s, 1H), 4.88 (s, 1H) 8.18–8.22 (m, 2H), 8.26–8.30 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 19.1, 23.2, 28.2, 29.1, 32.4, 41.2, 52.4, 63.6, 110.1, 123.5, 130.7, 135.8, 144.8, 150.5, 164.8; IR (neat): ν_{max} = 2953, 2868, 1724, 1528, 1474, 1348, 1269, 1115, 1101, 891, 716 cm^{-1}; 80% ee; HPLC analysis (AD–3, flow rate 1.00 ml/min, solvent: hexane/2–propanol = 300/1) t_R(racemic) = 14.77 min and 15.70 min. t_R[(1*R*,2*S*)–form] = 14.97 min.

23': pale yellow crystals; mp 54 –57 ºC; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.30 (s, 3H), 1.47 (s, 3H), 1.59 (s, 3H), 1.64–1.71 (m, 1H), 1.91–2.00 (m, 2H), 2.06–2.12 (m, 1H), 2.41–2.54 (m, 2H), 4.40–4.49 (m, 2H), 8.18–8.22 (m, 2H), 8.27–8.31 (m, 2H).

(+)-grandisol; 2-[(1*R*,2*S*)-1-Methyl-2-(prop-1-en-2-yl)cyclobutyl]ethan-1-ol (2)[20]



LiOH (11 mg, 0.44 mmol) in water (0.22 mL) was added to stirred solution of (1*R*,2*S*)–4–nitrobenzoate **23** (68 mg, 0.22 mmol) in THF (0.34 mL) at 0 –5 ºC under an Ar atmosphere, followed by being stirred at the same temperature for 14 h. The solution was diluted with Et_2O (0.70 mL) and CH_2Cl_2 (1.3 mL). Na_2SO_4 (180 mg) was added to the stirred mixture, followed by being stirred at the same temperature for 20 min. The mixture was filtered and the filtrate was concentrated under reduced pressure. The obtained crude oil was purified by SiO_2–gel column chromatography (hexane/AcOEt = 15 : 1) to give the desired product **2** (33 mg, 97%).

pale yellow oil; $[\alpha]_D^{25}$ +6.6 (*c* 1.0, $CHCl_3$) [lit.[20] $[\alpha]_D^{25}$ +6.9 (*c* 3, $CHCl_3$)]; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.18 (s, 3H), 1.42–1.47 (m, 1H), 1.55 (br s, 1H), 1.56–1.73 (m, 3H), 1.67 (s, 3H), 1.73–1.84 (m, 2H), 1.97 (m, 1H), 2.55 (t, *J* = 9.2 Hz, 1H), 3.63–3.72 (m, 2H), 4.65 (d, *J* = 1.2 Hz, 1H), 4.84 (d, *J* = 1.2 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 19.2, 23.2, 28.4, 29.3, 36.9, 41.3, 52.5, 60.0, 109.7, 145.2; IR (neat): ν_{max} = 3331, 2947, 2866, 1645, 1454, 1441, 1375, 1238, 1053, 1047, 1013, 1001, 883 cm^{-1}.

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Keywords: Synthetic methods; C-C coupling; Synthetic design; Norchrysanthemic acid; (+)-Grandisol

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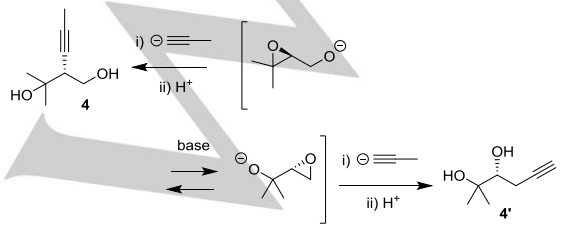

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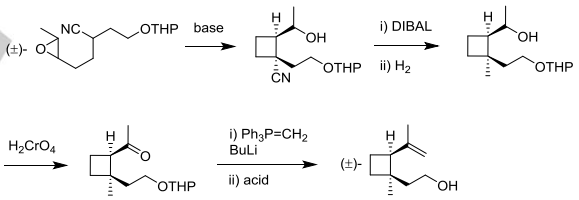

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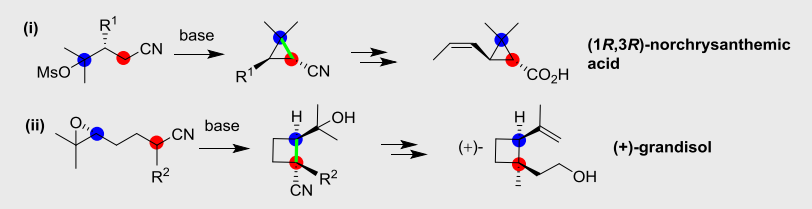

Chiral syntheses of two distinct small cycloalkanes, (1*R*,3*R*)-(1*Z*)-norchrysanthemic acid (7 steps, 23% overall yield) and (+)-grandisol (8 steps, 8% overall yield), were performed by common characteristic ring-closing methodologies using carbanions at the α-position of nitriles (nitrile α-anions).

*one or two words that highlight the emphasis of the paper or the field of the study

Chiral synthesis
Ring-closing cycloalkane formation

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Ring-Closing Strategy Utilizing Nitrile α-Anions: Chiral Synthesis of (+)-Norchrysanthemic Acid and Expeditious Asymmetric Total Synthesis of (+)-Grandisol