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Enantioselective synthesis of 2-allyl and 2-(3-trimethylsilylpropargyl)-2-hydroxycyclohexanone using osmium-catalyzed asymmetric dihydroxylation

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Abstract

The catalytic asymmetric dihydroxylation of (1-cyclohexenyl) or (1-cyclopentenyl) acetonitrile **5** and **15** with AD-mix-β occurred with good enantiofacial selectivity (87 to 94.7% ee after recrystallization) giving (*R,R*)-diols in agreement with the mnemonic device. The 6-membered ring diol nitrile was easily transformed, *via* standard functional group manipulations, to 2-allyl and 2-(3-trimethylsilylprop-2-ynyl)-2-hydroxycyclohexanone in about 35% overall yield. © 1998 Elsevier Science Ltd. All rights reserved.

1. Introduction

In pursuit of the total synthesis of histrionicotoxin **1**, a potent noncompetitive blocker of neuromuscular nicotinic channels,[1,2] we recently reported an efficient method to prepare enantioenriched α-allyl or propargyl-α-aminocyclohexanone **2a** and **2b**, good candidates for the elaboration of the 2-substituted-1-azaspiro[5.5]undecane ring system of **1**.[3] This methodology involves a benzilic-type rearrangement of tertiary α-hydroxyimines **3a** and **3b** and proceeds by a 1,2-suprafacial shift and complete chiral transmission (Scheme 1).[3c,d] The potential of this process was demonstrated by the concise formal *synthesis of (−)-perhydrohistrionicotoxin,*[3d] *a hydrogenation product of* **1**, *which like* **1** *is an important* biochemical tool for the study of the mechanism of action of cholinergic agonists in the neuromuscular *system.*[4]

As shown in Scheme 2, we first developed a synthesis of (*R*)-α-ketols **4a** and **4b**, precursors of compounds **3a** and **3b** involving a flash-chromatography resolution of diastereomeric ketals for **4a** or esters for **4b**.[3e] Depending of the substrate, this method presents several drawbacks: (1) in the case

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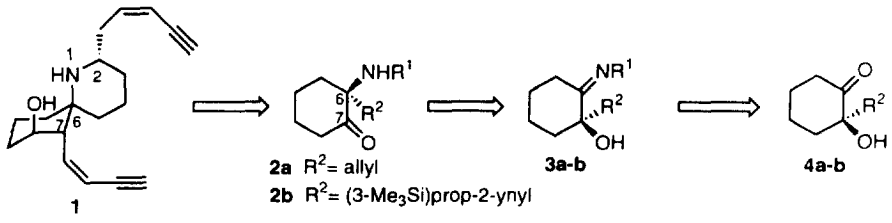
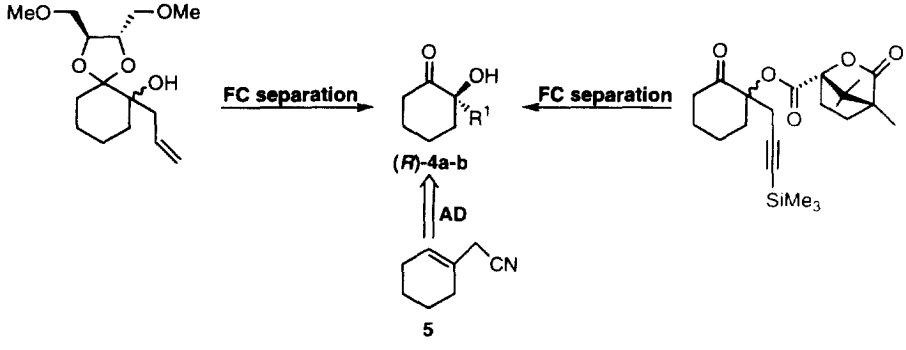


Scheme 1.

of **4a**, the efficiency of the chromatographic separation was low ($\Delta Rf=0.05$) and partial racemization occurred during acid deketalization *via* 1,2-migration of the allyl group[5]; (2) formation of (±)-**4b** from 1,2-cyclohexanedione is a low-yielding process.[3e] For these reasons, we searched for a more convenient and practical asymmetric synthesis of α-ketols **4a** and **4b**.



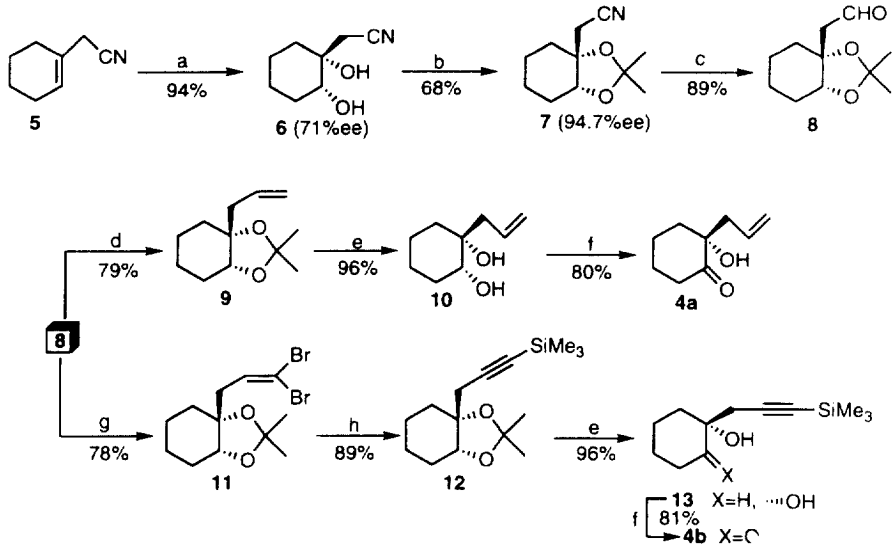
Scheme 2.

Herein, we report the synthesis of enantioenriched α-ketols **4a** and **4b** based on a reagent-control strategy of the stereochemistry. Because α-ketols **4a** and **4b** can obviously arise from their corresponding 1,2-diols, the Sharpless catalytic asymmetric dihydroxylation (AD)[6] of a substituted cyclohexene was used to introduce enantioselectively the quaternary stereogenic center of **4a** and **4b**. If a large number of examples of the AD reaction have appeared in the literature[6,7] only very few concern 1-substituted cyclohexene derivatives. Enantioselectivity in the AD reaction of this type of cycloolefin is quite variable ranging from 14 to 48% ee with those bearing bulky substituents[8] to near 100% with 1-phenyl or 1-[(p-methoxybenzoyloxy)methyl]-1-cyclohexene.[6,9]

Compound **5** bearing a nitrile function, commercially available and cheap, was identified by us as a perfect precursor for α-ketols **4a** and **4b**.

2. Results and discussion

The AD reaction of the unsaturated nitrile **5** using AD-mix-β was rather sluggish giving the diol **6** in 65% yield after three days at room temperature. However, addition of 0.4 mol% of osmium tetroxide and 1 equivalent of methanesulfonamide to the reaction mixture increased dramatically the rate of the reaction (8 h, 0°C) and improved the yield.[10] The diol **6** was thus obtained in 94% yield and 71% ee (determined by chiral GC after protection as an acetonide). The acetonide **7** could be obtained in almost pure enantiomeric form after two recrystallizations in hexane (94.7% ee, 70% yield). Reduction of the nitrile **7** took place smoothly at room temperature, in the presence of an excess of DIBAL-H to give the aldehyde **8** in 89% yield (Scheme 3).

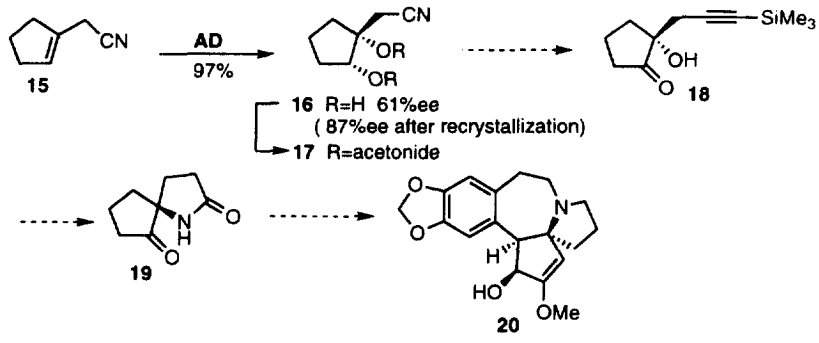


Scheme 3. Reagents and conditions: (a) AD-mix-β, OsO_4 (0.4 mol%), $MeSO_2NH_2$ (1 equiv.), t-BuOH:H_2O (1:1), 0°C, 8 h; (b) 2-methoxypropene, camphorsulfonic acid, THF, RT, 90 min; (c) DıBAL-H, THF, RT, 14 h; (d) CH_2I_2 (10 equiv.), Zn (30 equiv.), Zn (30 equiv.), Me_3Al (2 equiv.), THF, RT, 20 min then **8**, −20°C→RT; (e) 2 N HCl:MeOH (4:1), RT, 4 h; (f) *o*-iodoxybenzoic acid (IBX) (2.5 equiv.), DMSO, RT, 6 h; (g) PPh_3 (3 equiv.), **8** then CBr_4 (1.5 equiv.), CH_2Cl_2, −20°C→RT, 1 h; (h) *n*-BuLi (2 equiv.), Me_3SiCl, THF, −78°C→RT (3 h)

At this stage, our goal became the introduction of the terminal olefinic and silylated acetylenic functionalities. A Wittig reaction between aldehyde **8** and methylene triphenylphosphorane afforded the olefin **9** in 43–52% yield. The yield of the methylenation reaction was greatly increased by means of the CH_2I_2–Zn–$AlMe_3$ system[11] (79% yield). Acid hydrolysis of the acetonide protecting group followed by oxidation with *o*-iodoxybenzoic acid (IBX) in methyl sulfoxide[12] yielded the desired (*R*)-ketol **4a** in 77% yield for the two steps. The absolute configuration of **4a**[13] confirmed the enantiofacial selectivity of the AD reaction of **5** predicted by a mnemonic device proposed by Sharpless et al.[10a] We next focussed our attention on the formation of α-ketol **4b** bearing a 3-trimethylsilylpropargyl grouping. To this goal, aldehyde **8** was converted to the dibromo-olefin **11** by the Corey–Fuchs reaction[14] in 78% yield. Treatment of **11** with 2 equivalents of *n*-BuLi followed by an excess of chlorotrimethylsilane afforded the alkynylsilane **12** in 89% yield. Acid-catalyzed removal of the isopropylidene group followed by oxidation with IBX in methyl sulfoxide completed the synthesis of α-ketol **4b** in 78% yield.[13]

As an extension of the above described methodology, we studied the asymmetric dihydroxylation of commercially available (1-cyclopentyl) acetonitrile **15**. Under the same reaction conditions as for the corresponding 6-membered ring olefin **5**, the enantiofacial selectivity of the AD reaction on **15** slightly decreased in comparison to that of compound **5** (61% ee *versus* 71% ee). Moreover, the sense of π-facial discrimination of the AD reaction on **15** is very likely the same as for its corresponding 6-membered ring analog **5**. Recrystallization of the diol **16** in dichloromethane–hexane increased its enantiomeric purity to 87% (conditions not optimized). The diol **16** is potentially a valuable intermediate of spirolactam **19**, a precursor of cephalotaxin **20**,[15] *via* the homopropargylic alcohol **18** (Scheme 4).[16]

In summary, the AD reaction allowed a simple and practical preparation of enantioenriched α-ketols **4a** and **4b**. Starting from cheap 1-(cyclohexenyl)acetonitrile **5**, α-ketols **4a** and **4b** were respectively obtained in 35 and 31% yield. Further studies directed towards the synthesis of the precursor of cephalotaxin, lactam **19**, are currently underway.



Scheme 4.

3. Experimental

3.1. General procedures

^{1}H NMR spectra were recorded in $CDCl_3$ (δ_H=7.25) at ambient probe temperature on a Bruker AC 200 (200 MHz) spectrometer. Data are presented as follows: chemical shift (in ppm on the δ scale relative to δ_{TMS}=0), multiplicity (s=singlet, d=doublet, t=triplet, m=multiplet, br=broad), integration, coupling constant and interpretation. ^{13}C NMR spectra were recorded at ambient probe temperature on a Brucker AC 200 (50.3 MHz) in $CDCl_3$ used as the reference (δc=77.0). IR were recorded on a Perkin–Elmer 298 spectrophotometer. Optical rotations were measured on a Perkin–Elmer 141 polarimeter at the sodium D line (589 nm). Melting points were determined on a Büchi 530 apparatus and are uncorrected. Enantiomeric excesses were determined by GC using a Shimadzu GC.14A apparatus on a Lipodex E.MN column (25 m×0.25 mm). Combustion analyses were performed by the Service Central de Microanalyse, CNRS, Solaize.

Reagents and solvents were purified by standard means. Tetrahydrofuran was distilled from sodium wire/benzophenone and stored under a nitrogen atmosphere. Dichloromethane and methyl sulfoxide were distilled from calcium hydride. Methanol was distilled from magnesium metal. All other chemicals were used as received. Unless otherwise stated, all experiments were performed under anhydrous conditions in an atmosphere of nitrogen.

3.2. (1R,2R)-(1,2-Dihydroxycyclohexyl) acetonitrile 6

A mixture of *tert*-butyl alcohol (70 ml), water (70 ml), AD-mix-β (20 g) and methane sulfonamide (1.36 g, 14.3 mmol) was stirred for a few minutes at room temperature until two clear phases were produced. After addition of osmium tetroxide (4 wt% in water, 0.36 ml, 0.06 mmol), the mixture was cooled to 0°C and (1-cyclohexenyl) acetonitrile (1.73 g, 14.3 mmol) was added. The mixture was stirred for 8 h at 0°C. Sodium metabisulfite (14 g) was added and after stirring the mixture for 1 h at 0°C, dichloromethane (120 ml) was added. The aqueous phase was extracted twice with dichloromethane (120 ml). The combined organic extracts were dried ($MgSO_4$) and evaporated to dryness. The residue was purified by flash-chromatography on silica gel (Et_2O:petroleum ether, 3:2) to give **6** as a white solid (2.1 g, 94% yield). M.p. 95–101°C; $[\alpha]_D^{20}$ −1.6 (*c* 1, $CHCl_3$) (66% ee); IR (KBr) 2980, 2930, 2860, 2240 cm^{-1}; ^{1}H NMR: 1.3–1.8 (m, 7H), 2.0 (m, 1H), 2.58 (d+brs, 2H, J=17 Hz, CH_2CN, OH), 2.73 (d+brs, 2H, J=17 Hz, CH_2CN, OH), 3.52 (dd 1H, J=4.4 and 10.3 Hz, C*H*OH); ^{13}C NMR: 20.6, 23.7, 28.8, 30.4, 34.6, 72.1, 72.7, 117.9; anal. calcd for $C_8H_{13}NO_2$: C, 61.91; H, 8.44; N, 9.02. Found: C, 61.79; H, 8.64; N, 9.02.

3.3. (1R,2R)-[(1,2-Isopropylidenedioxy)cyclohexyl]acetonitrile 7

To a solution of the diol **6** (1.95 g, 12.56 mmol) in tetrahydrofuran (40 ml) was successively added camphorsulfonic acid (0.04 g) and 2-methoxypropene (2.72 ml, 25.1 mmol). The reaction was stirred for 90 min. at room temperature. After concentration *in vacuo*, the residue was chromatographed on silica gel (Et_2O:petroleum ether, 1:3) to afford **7** as a white solid (2.37 g, 97% yield). The enantiomeric excess (71%) was determined by GC analysis: nitrogen (carrier gas); temp. 80–150°C (5°C/min); retention time (min): 19.25 for (*S*)-7 and 19.69 for (*R*)-7. Two recrystallizations in hexane gave **7** (1.68 g) with an enantiomeric excess of 94.7%. M.p. 55–60°C; $[\alpha]_D^{20}$ −27.6 (*c* 0.7, $CHCl_3$) (94.7% ee); IR (KBr) 2980, 2930, 2860, 2240, 1360, 1340 cm^{-1}; ^1H NMR: 1.32 (s, 3H, CH_3), 1.5 (s, 3H, CH_3), 1.1–1.7 (m, 7H), 2.1–2.2 (m, 1H), 2.58 (d, 1H, J=17 Hz, CH_2CN), 2.67 (d, 1H, J=17 Hz, CH_2CN), 4.1 (brs, 1H, $CHOCMe_2$); ^{13}C NMR: 19.5, 22.6, 25.5, 26.2, 26.8, 28.3, 34.6, 76.0, 77.2, 108.3, 116.9; anal. calcd for $C_{11}H_{17}NO_2$: C, 67.66; H, 8.77. Found: C, 67.17; H, 8.82.

3.4. (1R,2R)-[(1,2-Isopropylidenedioxy)cyclohexyl]acetaldehyde 8

To a solution of the nitrile **7** (1 g, 5.1 mmol) in tetrahydrofuran (20 ml), cooled to −78°C, was added dropwise DIBAL-H (1 M in hexane, 14.4 ml). The reaction mixture was stirred for 14 h at room temperature, cooled to 0°C and 2 N HCl solution (5 ml) was added. After stirring for 20 min, the solution was filtered on a pad of silica gel (Et_2O:petroleum ether, 3:7). The filtrate was concentrated under reduced pressure to give the aldehyde **8** as an oil (0.895 g, 89% yield), which was used for the next step without further purification. IR (neat) 2980, 2930, 2860, 2730, 1730, 1360, 1340 cm^{-1}.

3.5. (1R,5R)-1-Allyl-3,3-dimethyl-2,4-dioxabicyclo[4,3,0]nonane 9

A tetrahydrofuran solution (15 ml) of diiodomethane (1.2 ml, 14.9 mmol), zinc (3 g, 45.8 mmol) and trimethylaluminium (2 M in THF, 1.51 ml, 3 mmol) was stirred at room temperature for 20 min. The solution was then cooled down to −20°C and the aldehyde **8** (0.3 g, 1.51 mmol) in tetrahydrofuran (2 ml) was added. The reaction mixture was slowly warmed up to room temperature (2 h), cooled to 0°C and quenched with a saturated NH_4Cl solution (5 ml). Extraction with ether, drying ($MgSO_4$) and evaporation of the organic extracts gave a residue which was purified by column chromatography on silica gel (Et_2O:petroleum ether, 3:97) to afford the olefin **9** as an oil (0.23 g, 79% yield). $[\alpha]_D^{20}$ −19.5 (*c* 2, $CHCl_3$); IR (neat) 3060, 2990, 2980, 2930, 1640, 1360 cm^{-1}; ^1H NMR: 1.3 (s, 3H, CH_3), 1.5 (s, 3H, CH_3), 1.1–1.7 (m, 7H), 2–2.1 (m, 1H), 2.32 (dd, J=6.8 and 16 Hz, CH_2–CH=CH_2), 2.40 (dd, J=6.8 and 16 Hz, CH_2–CH=CH_2), 3.9 (brs, 1H, $CHOCMe_2$), 5.0–5.13 (m, 2H, CH=CH_2), 5.9 (ddt, 1H, J=6.8, 10.5 and 17 Hz, CH=CH_2); ^{13}C NMR: 19.8, 22.7, 26.2, 27.0, 28.5, 34.3, 40.2, 76.3, 80.1, 106.8, 117.7, 133.9.

3.6. (1R,2R)-1-Allyl-1,2-cyclohexanediol 10

A solution of the acetonide **9** (0.2 g, 1 mmol) in methanol:2 N HCl (4:1) was stirred for 4 h at room temperature. The solution was concentrated under reduced pressure and the residue was purified by chromatography on silica gel (Et_2O:petroleum ether, 3:2) to yield the diol **10** (0.152 g, 96% yield) obtained as a white solid. M.p. 70–72°C; $[\alpha]_D^{20}$ +2.9 (*c* 1.6, $CHCl_3$); IR (KBr) 3400, 2980, 2930, 2860, 1640 cm^{-1}; ^1H NMR: 1.4–1.8 (m, 8H, $4CH_2$), 2.38 (dd, 1H, J=6.7 and 15.5 Hz, CH_2–CH=CH_2), 2.51 (dd, J=6.7 and 15.5 Hz, CH_2–CH=CH_2), 3.7 (brt, 1H, J=5.7 Hz, $CHOH$), 5.1–5.3 (m, 2H, CH=CH_2),

5.9 (ddt, 1H, J=6.7, 10.5, 17 Hz, C*H*=CH_2); ^{13}C NMR: 21.1, 23.3, 30.4, 34.4, 43.7, 73.4, 118.8, 133.9; anal. calcd for $C_9H_{16}O_2$: C, 69.19; H, 10.32. Found: C, 68.75; H, 10.30.

3.7. (2R)-2-Allyl-2-hydroxycyclohexanone ***4a***

To a solution of *o*-iodoxybenzoic acid (IBX)[12a,b] (0.46 g, 2.5 equiv.) in methyl sulfoxide (6 ml) was added the diol **10** (0.1 g, 0.64 mmol) in methyl sulfoxide (3 ml). The solution was stirred for 6 h at room temperature, cooled to 0°C and quenched by water (20 ml). The precipitate (iodosobenzoic acid) was filtered and the filtrate was extracted with dichloromethane (3×20 ml). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed on silica gel (Et_2O:petroleum ether, 1:4) to give the α-ketol **4a** as a yellow oil (0.079 g, 80% yield). $[\alpha]_D^{20}$ −146.8 (*c* 1.1, $CHCl_3$), [lit. −139.2 (*c* 1.2, $CHCl_3$), 89% ee].[3c] Its spectroscopic data were identical to those reported in the literature.[3e]

3.8. (1R,5R)-1-(3,3-Dibromo)allyl-3,3-dimethyl-2,4-dioxabicyclo[4.3.0]nonane ***11***

To a dichloromethane solution (10 ml) containing triphenylphosphine (1.63 g, 6.23 mmol) and the aldehyde **8** (0.41 g, 2.1 mmol), cooled to −20°C, was added carbon tetrabromide (1.03 g, 3.12 mmol) in dichloromethane (5 ml). After stirring the reaction mixture for 1 h at room temperature, a mixture of ether:petroleum ether (10 ml, 1:9) was added. The suspension (PPh_3O) was filtered on silica gel (Et_2O:petroleum ether, 1:9) to afford the dibromo-olefin **11** (0.58 g, 78%) as an oil. $[\alpha]_D^{20}$ −16.9 (*c* 1.6, $CHCl_3$); IR (neat) 3030, 2980, 2930, 2860, 1630, 1360, 1340 cm^{-1}; ^{1}H NMR: 1.3 (s, 3H, CH_3), 1.5 (s, 3H, CH_3), 1.1–1.8 (m, 7H), 2.05–2.2 (m, 1H), 2.4 (d, 2H, J=7.3 Hz, CH_2CH=CBr_2), 3.85 (brs, 1H, C*H*OCMe_2), 6.58 (t, 1H, J=7.3 Hz, C*H*=CBr_2); ^{13}C NMR: 19.8, 22.8, 26.4, 26.8, 28.4, 34.5, 39.0, 76.3, 79.8, 90.4, 107.3, 134.9; anal. calcd for $C_{12}H_{18}Br_2O_2$: C, 40.7; H, 5.12. Found: C, 40.98; H, 5.14.

3.9. (1R,5R)-3,3-Dimethyl-1-(3-trimethylsilylprop-2-ynyl)-2,4-dioxabicyclo[4,3,0]nonane ***12***

To a cooled solution (−78°C) of the dibromo-olefin **11** (0.51 g, 1.44 mmol) in tetrahydrofuran (7 ml) was added *n*-BuLi (2.3 M in hexanes, 1.24 ml, 2 equiv.). After stirring for 1 h at −78°C, chlorotrimethylsilane was added (0.55 ml, 4.3 mmol). The reaction mixture was stirred for 3 h at room temperature, concentrated *in vacuo* and the residue purified by flash column chromatography on silica gel (Et_2O:petroleum ether, 1:9) to give **12** as a yellow oil (0.34 g, 89% yield). $[\alpha]_D^{20}$ −30.9 (*c* 1.6, $CHCl_3$); IR (neat) 2990, 2940, 2860, 2180, 1360, 1340 cm^{-1}; ^{1}H NMR: 0.15 (s, 9H, $SiMe_3$), 1.37 (s, 3H, CH_3), 1.45 (s, 3H, CH_3), 1.5–1.7 (m, 7H), 2–2.15 (m, 1H), 2.5 (s, 2H, CH_2–C≡C$SiMe_3$), 4.2 (brs, 1H, C*H*OCMe_2); ^{13}C NMR: 0.1, 19.6, 22.8, 26.3, 26.9, 28.0, 28.3, 35.3, 75.6, 79.0, 87.3, 103.4, 107.8.

3.10. (1R,2R)-1-(3-Trimethylsilylprop-2-ynyl)-1,2-cyclohexanediol ***13***

The acetonide hydrolysis of compound **12** (0.23 g) was effected according to the protocol used for **9**. The diol **13** was obtained as a white solid in 96% yield. M.p. 94–96°C; $[\alpha]_D^{20}$ −26.4 (*c* 0.9, $CHCl_3$); IR (KBr) 3400, 2980, 2930, 2860, 2180 cm^{-1}; ^{1}H NMR: 0.15 (s, 9H, $SiMe_3$), 1.1–1.9 (m, 8H, 4CH_2), 2.4 (brs, 2H, OH), 2.48 (d, 1H, J=17 Hz, CH_2C≡C$SiMe_3$), 2.6 (d, 1H, J=17 Hz, CH_2C≡C$SiMe_3$), 3.6 (dd, 1H, 4 and 9.7 Hz, C*H*OH); ^{13}C NMR: 0.15, 21.1, 23.8, 30.4, 31.4, 34.8, 72.7, 73.0, 88.5, 103.4; anal. calcd for $C_{12}H_{22}O_2Si$: C, 63.6; H, 9.79. Found: C, 63.1; H, 9.75.

3.11. (2R)-2-(3-Trimethylsilylprop-2-ynyl)-2-hydroxycyclohexanone **4b**

The diol **13** (0.123 g) was oxidized by IBX by the same protocol as for **10**. Compound **4b** was obtained as a yellow oil in 81% yield. $[\alpha]_D^{20}$ −92.3 (*c* 1, $CHCl_3$), [lit. $[\alpha]_D^{20}$ −93 (*c* 1.3, $CHCl_3$) >96% ee].[3e] Its spectroscopic data were found to be identical to those reported in the literature.[3e]

3.12. (1R,2R)-(1,2-Dihydroxycyclopentyl)acetonitrile **16**

The AD reaction on **15** (0.53 g, 4.94 mmol) was effected according to the protocol described for compound **5**. The diol **16** was obtained as a white solid in 97% yield (87% ee after two recrystallizations from dichloromethane–hexane). M.p. 70–72°C; $[\alpha]_D^{20}$ −15 (*c* 1, $CHCl_3$) (87% ee); IR (KBr), 3400, 3020, 2920, 2240 cm^{-1}; ^1H NMR: 1.4–2.1 (m, 6H), 2.56 (d, 1H, J=17 Hz, CH_2CN); 2.66 (d, 1H, J=17 Hz, CH_2CN), 3.95 (t, 1H, J=7.3 Hz, C*H*OH). ^{13}C NMR: 19.0, 27.7, 31.7, 35.7, 76.4, 76.7, 117.8.

3.13. (1R,2R)-[(1,2-Isopropylidenedioxy)cyclopentyl]acetonitrile **17**

The diol **16** (0.7 g) was protected as an acetonide by the same procedure as for compound **6**. The acetonide **17** (0.76 g) was obtained as an oil in 87% yield. $[\alpha]_D^{20}$ +45 (*c* 1.2, $CHCl_3$) (61% ee). The enantiomeric excess was determined by chiral GC analysis: nitrogen (gas carrier); temp. 80–150°C (4°C/min); retention time (min): 13.03 for (*S*)-**17** and 13.37 for (*R*)-**17**. ^1H NMR: 1.37 (s, 3H, CH_3), 1.42 (s, 3H, CH_3), 1.5–2.0 (m, 6H, 3CH_2), 2.68 (d, 1H, J=16 Hz, CH_2CN), 2.73 (d, 1H, J=16 Hz, CH_2CN), 4.47 (d, 1H, J=4.5 Hz, C*H*OCMe$_2$); ^{13}C NMR: 23.2, 26.4, 27.2, 28.2, 33.3, 38.6, 85.3, 88.3, 110.7, 117.2.

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