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STEREOSELECTIVE REACTIONS. 15.[1] TOTAL SYNTHESIS OF (+)-IVALIN BY UTILIZING ASYMMETRIC DOUBLE ALKYLATION REACTION OF α,β-UNSATURATED ALDIMINE

Kiyoshi Tomioka, Fumio Masumi,[2] Toyoharu Yamashita, and Kenji Koga*

Faculty of Pharmaceutical Sciences, University of Tokyo,
Hongo, Bunkyo-ku, Tokyo 113, Japan

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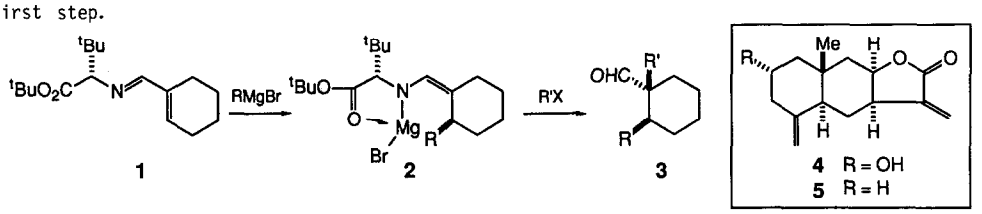
An asymmetric total synthesis of (+)-ivalin (**4**), a representative of antileukemic eudesmane sesquiterpenes, is described. The ene-aldehyde (**6**) was converted to the nearly optically pure alcohol (**20**) through the asymmetric double alkylation reaction of the chiral ene-enamine (**14**). The ene-carbonyl cyclization of (**25**) with tin(IV) chloride afforded the core skeleton (**26**). The stereoinversion of hydroxyl group and further transformation furnished (+)-ivalin (**4**).

An area of challenging current researches is the development of asymmetric reactions useful in the total synthesis of biologically active chiral compounds.[3] In our studies directed toward such area we exploited the asymmetric double alkylation reaction of α,β-unsaturated cyclic aldimines (**1**) to produce highly optically pure trans-1,2-disubstituted cycloalkanecarboxaldehydes (**3**) with predictable absolute configuration.[4,5]

This new reaction is constituted from two consecutive stereoselective carbon-carbon bond forming reactions; the first step is the nucleophilic conjugate addition of Grignard reagent to chiral α,β-unsaturated aldimine (**1**) affording 2-substituted magnesioenamine (**2**), the second step is the in situ alkylation of **2** with alkyl halide affording **3**, after hydrolysis. The reaction is quite unique and useful in the two points that a nucleophile is introduced in a high diastereoselectivity and an electrophile is introduced cis to the nucleophile introduced in the first step.

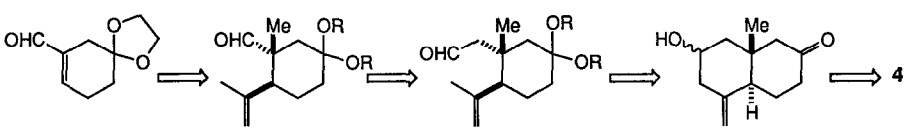


1 **2** **3**

Since the antileukemic eudesmane sesquiterpenes such as ivalin (**4**)[6,7] and alantolactone (**5**) have been the targets of considerable synthetic efforts,[8~10] this type of natural products appear particularly interesting as a touchstone for demonstration of the new asymmetric reactions. We describe the detail of the first asymmetric total synthesis of (+)-ivalin (**4**).[11]

Synthetic Design

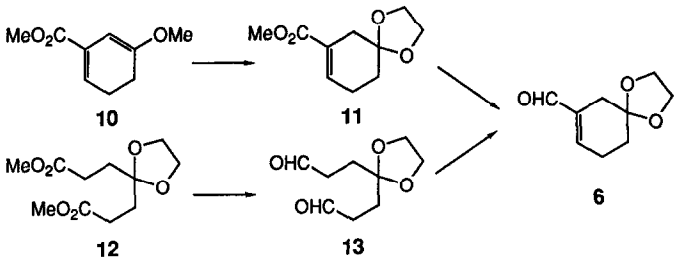
The synthetic approach under consideration involves three key stages, asymmetric synthesis of trans-1,2-disubstituted cyclohexanecarboxaldehyde (**7**) from **6** by applying our new asymmetric double alkylation reaction, the intramolecular ene-carbonyl cyclization of **8** to construct the methyldecaline unit (**9**), then elaboration of **9** to attach exo-methylenelactone part.



6 **7** **8** **9**

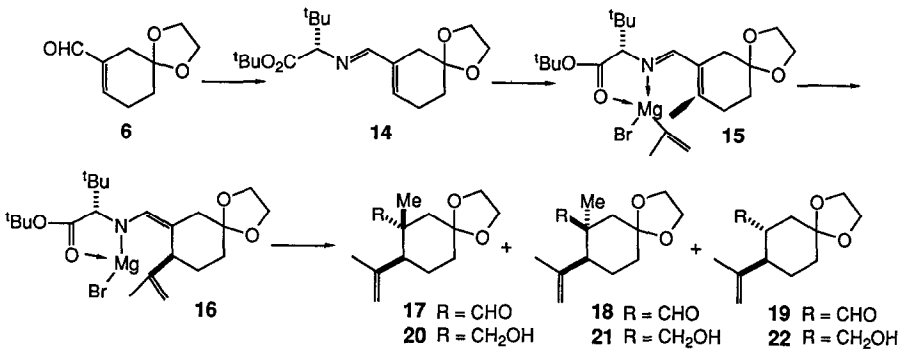
Synthesis of Ene-Aldehyde (6)

Two synthetic routes to **6** were investigated. Birch reduction of ortho-methoxybenzoic acid[12] and following esterification with diazomethane provided **10** in 49% overall yield. Ketalization[13] of **10** with ethyleneglycol afforded **11**, which was then converted to **6** via reduction-reoxidation sequence in 60% overall yield. Alternatively, DIBAH reduction of **12**[14] and following aldol condensation of **13** provided **6** in 25% yield in one pot operation. In a large scale preparation, we adopted the former procedure.



Asymmetric Double Alkylation Reaction of 14

The requisite ene-imine (**14**) was prepared by the condensation of **6** with L-tert-leucine tert-butyl ester[15] in refluxing benzene in a quantitative yield. Double alkylation reaction of **14** with isopropenylmagnesium bromide in tetrahydrofuran (THF) and then with six equivalents of methyl iodide in the presence of five equivalents of hexamethylphosphoric amide (HMPA) afforded, after hydrolysis, a mixture of aldehydes (**17**∿**19**). Without purification the mixture was subjected to sodium borohydride reduction in methanol to give a mixture of easily separable alcohols. The trans-alcohol (**20**) was isolated in 35% overall yield as a major product, along with the cis-alcohol (**21**) and non-methylated alcohol (**22**) in 22 and 20% yields, respectively.



The methylation step was highly sensitive to the amount of HMPA and the use of fifteen equivalents of HMPA lead to the formation of **20**, **21**, and **22** in a ratio of 1:4:10.[16] Although the presence of HMPA is essential in the methylation reaction, the reason of the decreasing methylation products with the increase of the amount of HMPA is obscure.

The relative configurations of **20** and **21** were determined by ^{13}C-NMR analysis of the corresponding aldehydes (**17** and **18**),[17] and further confirmed by the conversion of **20** into (+)-ivalin (**4**). In the ^{13}C-NMR, signal of the angular methyl group of **17** appeared at 11.0 ppm, while that of **18** at 22.6 ppm. This indicates clearly that **17** has the axial angular methyl group which showed the steric compression effect.[5]

Although the diastereoselectivity of the double alkylation reaction was not so high, the enantioselectivity of the reaction was found to be as high as 95% by converting **20** to the

crystalline nitrile (**24**). Repeated recrystallization from hexane of the nitrile (**24**) (mp 39-41 °C, $[\alpha]_D^{20}$ +19.0 °($CHCl_3$)), obtained without fractionation by purification through column chromatography of the crude products, afforded the optically pure **24** of constant optical rotation (mp 42-43 °C, $[\alpha]_D^{20}$ +20.1 °($CHCl_3$)) in 80% recovery. This means that the asymmetric double alkylation reaction afforded **17** in 95% ee. In accord with the prediction from the stereochemical course of the reaction as shown in **15** and **16**, the absolute configuration of **20** was proved by converting it into natural (+)-ivalin (**4**) of the definite absolute configuration.

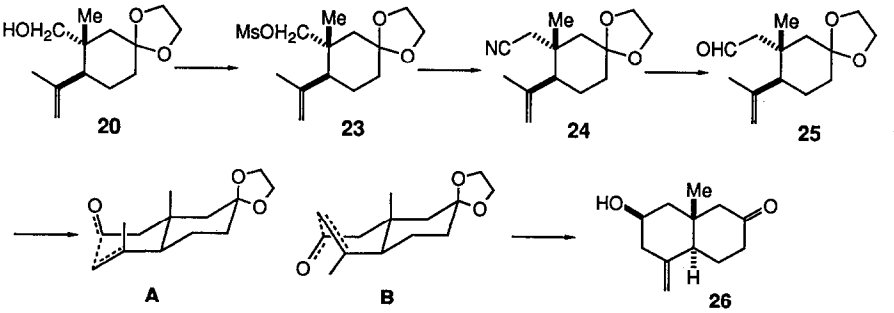
Synthesis of Methyldecaline Unit (26) by Ene-Carbonyl Cyclization

The alcohol (**20**) was mesylated with methanesulfonyl chloride to **23**, which was then treated with sodium cyanide in HMPA at 120 °C to afford the nitrile (**24**).[18] Then **24** of 95% ee was recrystallized from hexane to afford the optically pure **24** in 64% overall yield from the alcohol (**20**). Then **24** was reduced with DIBAH in ether to afford the aldehyde (**25**) in 88% yield.

Ene-carbonyl cyclization of **25** with tin(IV) chloride[19] in methylene chloride resulted in the concomitant deprotection of the ethyleneacetal group to afford selectively the decaline unit (**26**) in 61% yield.

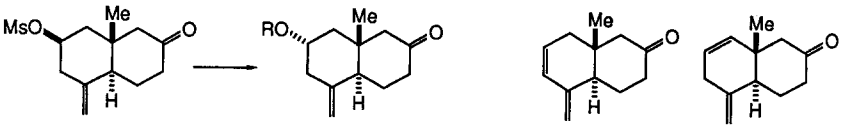
The axial orientation of the hydroxy group in **26** was suggested by ^{1}H-NMR. The C2-H appeared at 4.20 ppm with a half width of 11 Hz, corresponding to axial orientation of C2-OH. This was also ascertained by the NMR of **28** with the reversed configuration at the C-2 center in which C2-H appeared at 3.80 ppm with a half width of 20 Hz corresponding to axial proton.[6a]

The selective formation of **26** was attributed to the favorable transition state **A** in which the developing six membered carbocycle could attain the chair conformation, while transition state **B** leading to **28** requires the boat conformation.



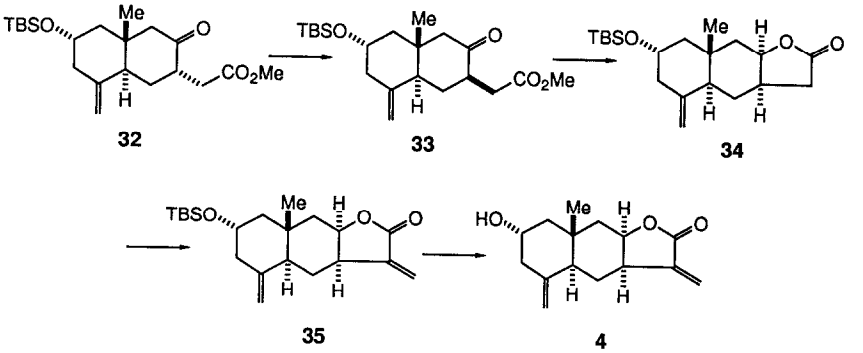
Stereoinversion of the Hydroxy group of 26

Although the elimination reaction leading to **30** and **31** was the major course of the reactions attempted,[20] the desired alcohol **28** was obtained from **27** only by the Corey's method.[21] Thus, treatment of **27** with potassium superoxide in the presence of 18-crown-6 in dimethylsulfoxide-dimethoxyethane produced the alcohol (**28**), which was silylated to **29** in 20% overall yield from **26**.



Synthesis of (+)-Ivalin (4)

Direct introduction of acetic acid residue into **29** with LDA-methyl bromoacetate afforded **32** in 80% yield, which then easily epimerized to **33** in 76% yield. Sodium borohydride reduction and acidification afforded the lactone (**34**) in 81% yield. The construction of exo-methylene unit was carried out under the standard conditions[22] to provide **35** in 37% overall yield. Deprotection produced the crystalline (+)-ivalin (**4**) in 78% yield.



Optical rotation, spectroscopic data, melting point, mixed-melting point, and tlc behavior of the synthetic **4** were completely identical with those of the natural (+)-ivalin.

Conclusion

(+)-Ivalin (**4**) of natural absolute configuration was successfully synthesized. The synthesis of **4** revealed usefulness of the new asymmetric double alkylation reaction as well as the ene-carbonyl cyclization in forming the core skeleton of the eudesmane sesquiterpenes.

Acknowledgement: We are grateful to Professor Akio Karube, Akita Technical college, Japan, for kind donation of natural (+)-ivalin.

Experimental Section

Melting points were measured using a Büchi 510 melting point apparatus and are not corrected. Optical rotations were taken with a Jasco DIP-181 Digital Polarimeter. IR spectra were taken with a Jasco Infrared Spectrometer Model DS-402G. ^{1}H-NMR spectra were taken with a Hitachi R-24 Spectrometer at 60 MHz, or with a JNM-PS 100 Spectrometer, or with a JEOL FX-100 Spectrometer at 100 MHz. ^{13}C NMR spectra were taken with JEOL FX-100 Spectrometer at 25 MHz. Chemical shift values are expressed in ppm relative to internal tetramethylsilane. Abbreviations are as follows: s, singlet; d, doublet; t, triplet; m, multiplet. MS were taken with a JEOL DX-300 Mass Spectrometer.

Methyl 5-methoxy-1,5-cyclohexadiene-1-carboxylate (10)

To a solution of the Birch reduction product of o-methoxybenzoic acid[12] (18.9 g, 0.12 mol) in a mixture of methanol (90 ml) and ether (90 ml) was added an ether solution of diazomethane (from nitrosomethylurea (22.0 g, 0.21 mmol)). The mixture was concentrated to afford **10** (20.6 g, quant) as a pale yellow oil. NMR ($CDCl_3$) δ: 2.40 (4H, m, CH_2 x 2), 3.56 (3H, s, CH_3), 3.67 (3H, s, CH_3), 5.35 (1H, s, CH), 6.45 (1H, m, CH); IR (neat): 1710, 1640 cm^{-1}. MS m/z: 168 (M^+).

Methyl 5-ethylenedioxy-1-cyclohexene-1-carboxylate (11)

To a solution of **10** (7.77 g, 46.2 mmol) and ethylene glycol (3.87 ml, 69.3 mmol) in THF (70 ml) was added boron trifluoride etherate (1.17 ml, 9.24 mmol) under ice bath cooling.[13] The mixture was stirred at room temperature for 2 h. After the addition of satd. $NaHCO_3$ (40 ml), the mixture was concentrated and then extracted with ether. The combined extracts were washed with brine and dried over $MgSO_4$. Concentration afforded a yellow oil which was distilled (bp 90-100 °C/0.4 mmHg) to afford **11** as a colorless oil (8.65 g, 94%). NMR ($CDCl_3$) δ: 1.72 (2H, t, J=7 Hz, CH_2), 2.2-2.6 (4H, m, CH_2), 3.70 (3H, s, CH_3), 3.95 (4H, s CH_2 x 2), 6.95 (1H, m, CH); IR (neat): 1710, 1650 cm^{-1}; MS m/z: 198 (M^+).

5-Ethylenedioxy-1-cyclohexene-1-methanol

A mixture of **11** (19.2 g, 97.2 mmol) and lithium aluminum hydride (2.77 g, 73.0 mmol) in ether (150 ml) was stirred at room temperature for 1 h. Successive addition of water (2.77 ml), 15% aq. NaOH (2.77 ml) and water (8.31 ml) and then filtration followed by concentration afforded a pale yellow oil (17 g). Purification by silica gel column chromatography (ethyl acetate/hexane=1:1) afforded the corresponding alcohol (15.9 g, 96%) as a colorless oil. NMR ($CDCl_3$) δ: 1.70 (2H, t, J=6 Hz, CH_2), 2.2-2.6 (5H, m), 3.95 (6H, s, CH_2 x 3), 5.60 (1H, m, CH); IR (neat): 3430 cm^{-1}; MS m/z: 170 (M^+).

5-Ethylenedioxy-1-cyclohexene-1-carboxaldehyde (6)

From the corresponding alcohol obtained as above: To a suspension of pyridinium chlorochromate (PCC)[23] (21.9 g, 101 mmol) and sodium acetate (8.31 g, 101 mmol) in methylene chloride (80 ml) was added a solution of the alcohol above (11.5 g, 67.6 mmol) in methylene chloride (60 ml) under ice bath cooling. The mixture was stirred at room temperature for 30 min and concentrated. The residue was diluted with ether (80 ml) and hexane (80 ml) and filtered through the pad of celite (545). The filtrate was concentrated and distilled (bp 80.0-84.0 °C/0.05 mmHg) to afford **6** (7.47 g, 66%) as a colorless oil. NMR ($CDCl_3$) δ: 1.80 (2H, t, J=6 Hz, CH_2), 2.2-2.8 (2H, m, CH_2), 2.40 (2H, s, CH_2), 3.95 (4H, s, $O(CH_2)_2O$), 6.75 (1H, m, CH), 9.40 (1H, s, CHO); IR (neat): 1680, 1640 cm^{-1}; MS m/z: 168 (M^+). Oxime was prepared and recrystallized from benzene. Mp 117-117.5 °C. Anal. Calcd for $C_9H_{13}NO_3$ C 59.00, H 7.15, N 7.65. Found C 58.91, H 7.18, N 7.54.

From **12**: To a solution of **12**[14] (1.02 g, 4.13 mmol) in toluene (10 ml) was added a hexane solution of DIBAH (5.2 ml, 9.14 mmol) at -78 °C and the mixture was stirred for 25 min. The mixture was poured into a cooled (ice bath) 20% aq. NaOH (10 ml) and stirred for 15 min. The mixture was diluted with brine (10 ml) and extracted with ethyl acetate. The combined extracts were successively washed with 5% aq. NaOH, 5% aqueous citric acid, satd. aq. $NaHCO_3$ and brine and dried over K_2CO_3. Concentration and purification through silica gel column chromatography (benzene/ethyl acetate=20:1) afforded **6** (170 mg, 25%).

(-)-N-(4-Methylenedioxycyclohexenyl-2-methylidene)-L-tert-leucine tert-butyl ester (14)

A solution of **6** (13.4 g, 80.0 mmol) and L-tert-leucine tert-butyl ester (15.3 g, 82.0 mmol) in benzene (200 ml) was azeotropically refluxed for 28 h. Concentration and recrystallization from water-ethanol (2:1) afforded **14** (27.1 g, quant) as pale yellow needles of mp 51-53 °C. $[\alpha]_D^{20}$ -88.6 °(c 1.00, benzene), NMR ($CDCl_3$) δ: 0.95 (9H, s, t-Bu), 1.42 (9H, s, t-Bu), 1.76 (2H, t, J=8 Hz, CH_2), 2.2-2.8 (4H, m, CH_2 x 2), 3.32 (1H, s, CH), 3.90 (4H, s, $O(CH_2)_2O$), 6.16 (1h, m, CH), 7.67 (1H, s, CHN); IR ($CHCl_3$): 1743, 1730, 1725 cm^{-1}; MS m/z: 337 (M^+). Anal. Calcd for $C_{19}H_{31}NO_4$ C 67.62, H 9.26, N 4.15. Found C 67.76, H 9.57, N 4.02.

(+)-(1R,2S)-5-Ethylenedioxy-2-isopropenyl-1-methyl-cyclohexane-1-methanol (20)

To a cooled (-23 °C) solution of **14** (18.0 g, 53 mmol) in THF (210 ml) was added a THF solution of isopropenylmagnesium bromide (76 ml, 160 mmol) and the whole was stirred for 5 h. A solution of methyl iodide (20 ml, 320 mmol) and HMPA (37 ml, 210 mmol) in THF (10 ml) was added and the mixture was stirred at -23 °C for 2 h and then at room temperature for 16 h. The mixture was poured into 10% aqueous citric acid (620 ml) under ice bath cooling and stirred for 1 h and then extracted with ethyl acetate. The combined extracts were washed with 10% aqueous $Na_2S_2O_3$, 10% citric acid, water, satd. $NaHCO_3$ and brine and then dried over $MgSO_4$. Concentration afforded a brown oil (12.8 g). A mixture of the oil and sodium borohydride (6.05 g, 160 mmol) in methanol was stirred at 0 °C for 20 min and then diluted with brine. The mixture was extracted with chloroform. The combined extracts were washed with brine and dried over K_2CO_3. Concentration and silica gel column chromatography (hexane/benzene/ethyl acetate=7:3:3) afforded **20** (4.19 g, 35%), **21** (2.68 g, 22%), and **22** (2.2 g, 20%).

20: A pale yellow oil. $[\alpha]_D^{20}$ +33.3 °(c 2.45, $CHCl_3$); NMR ($CDCl_3$) δ: 0.96 (3H, s, CH_3), 1.2-2.3 (11H, m), 3.21 and 3.35 (each 1H, d, J=10 Hz, CH_2OH), 3.92 (4H, m, $O(CH_2)_2O$), 4.72 (1H, m, CH), 4.84 (1H, m, CH); IR ($CHCl_3$): 3440 cm^{-1}; MS m/z: Calcd for $C_{13}H_{22}O_3$ 226.1568. Found 226.1535.

21: A pale yellow oil. $[\alpha]_D^{20}$ +8.13 °(c 2.94, $CHCl_3$); NMR ($CDCl_3$) δ: 0.90 (3H, s, CH_3), 1.2-2.2 (11H, m), 3.32 and 3.76 (each 1H, d, J=12 Hz, CH_2OH), 3.96 (4H, m, $O(CH_2)_2O$), 4.74 (1H, m, CH), 4.88 (1H, m, CH); IR ($CHCl_3$): 3440 cm^{-1}; MS m/z: Calcd for $C_{13}H_{22}O_3$ 226.1568. Found 226.1564.

(1R,2S)-5-Ethylenedioxy-2-isopropenyl-1-methyl-cyclohexane-1-methyl methanesulfonate (23)

To a cooled (0 °C) solution of **20** (3.88 g, 17.1 mmol) in methylene chloride (50 ml) was added pyridine (5.55 ml, 68.6 mmol), methanesulfonyl chloride (2.65 ml, 34.3 mmol), and diisopropylethylamine (8.96 ml, 51.4 mmol) and the mixture was stirred at room temperature for 30 min. The mixture was diluted with ethyl acetate and washed with 10% HCl, satd. $NaHCO_3$, and brine, and dried over $MgSO_4$. Concentration afforded **23** as a brown oil (5.62 g, quant). This was used in the next step without further purification. NMR ($CDCl_3$) δ: 1.02 (3H, s, CH_3), 1.0-2.4 (10H, m), 2.90 (3H, s, CH_3), 3.6-4.1 (6H, m, CH_2 x 3), 4.70 (1H, m, CH), 4.90 (1H, m, CH); IR ($CHCl_3$): 1360, 1170 cm^{-1}; MS m/z: Calcd for $C_{14}H_{24}O_5S$ 304.1341. Found 304.1338.

(+)-(1R,2S)-5-Ethylenedioxy-2-isopropenyl-1-methyl-cyclohexaneacetonitrile (24)

A solution of **23** (5.21 g, 15.7 mmol) and sodium cyanide (2.31 g, 47.1 mmol) in HMPA (50 ml) was stirred at 120 °C for 3 days and diluted with ethyl acetate. The mixture was washed with water, satd. $NaHCO_3$, and brine and dried over K_2CO_3. Concentration afforded a brown oil (4.04 g). Purification by silica gel column chromatography (benzene/ethyl acetate=50:1) afforded **24** (3.06 g, 83%) as colorless needles of mp 39-41 °C. $[\alpha]_D^{20}$ +19.0 °(c 0.849, $CHCl_3$); NMR ($CDCl_3$) δ: 1.10 (3H,

s, CH_3), 1.2-2.2 (10H, m), 2.23 (2H, s, CH_2CN), 3.90 (4H, m, $O(CH_2)_2O$), 4.80 (1H, m, CH), 4.92 (1H, m, CH); IR ($CHCl_3$): 2240 cm^{-1}; MS m/z: 235 (M^+). Anal. Calcd for $C_{14}H_{21}O_2N$ C 71.46, H 8.99, N 5.95. Found C71.73, H 9.06, N 5.86.

Repeated recrystallization from hexane afforded optically pure **24** of constant optical rotation in 80% recovery. Mp 42-43 °C. $[\alpha]_D^{20}$ +20.1 °(c 1.06, $CHCl_3$).

(+)-(1R,2S)-5-Ethylenedioxy-2-isopropenyl-1-methyl-cyclohexaneacetoaldehyde (25)

To a cooled (0 °C) solution of **24** (2.10 g, 8.92 mmol) in ether (150 ml) was added a hexane solution of DIBAH (10.2 ml, 17.8 mmol) and the mixture was stirred for 30 min. After the addition of satd. NH_4Cl (100 ml) the mixture was stirred for 1 h. After the addition of 5% H_2SO_4 (55 ml), the mixture was extracted with ether. The combined extracts were washed with water, satd. $NaHCO_3$, and brine and dried over $MgSO_4$. Concentration afforded **25** (1.88 g, 88%) as a colorless oil. This compound is not stable to silica gel column chromatography and used directly in the next step. $[\alpha]_D^{20}$ +34.9 °(c 1.64, $CHCl_3$); NMR ($CDCl_3$) δ: 1.22 (3H, s, CH_3), 1.5-2.3 (10H, m), 2.28 and 2.36 (each 1H, d, J=3 Hz, CH_2CHO), 3.90 (4H, m, $O(CH_2)_2O$), 4.68 (1H, m, CH), 4.88 (1H, m, CH), 9.72 (1H, t, J=3 Hz, CHO); IR ($CHCl_3$): 1710 cm^{-1}; MS m/z: Calcd for $C_{14}H_{22}O_3$ 238.1566. Found 238.1564.

(-)-(4aS,7R,8aR)-7-Hydroxy-5-methylene-8a-methyl-decahydronaphthalen-2-one (26)

To a cooled (-10 °C) solution of **25** (1.67 g, 7.0 mmol) in methylene chloride (700 ml) was added a solution of tin(IV) chloride (7.0 mmol) in methylene chloride (17.6 ml). The mixture was stirred at -10 °C for 2 h and at room temperature for 40 min. After the addition of satd. NH_4Cl, the mixture was extracted with chloroform. The combined extracts were washed with satd. $NaHCO_3$ and brine and then dried over $MgSO_4$. Concentration and purification by silica gel column chromatography (benzene/ethyl acetate=2:1) afforded **26** (1.18 g, 61%) as yellow needles. Mp. 100-102 °C (from hexane). $[\alpha]_D^{20}$ -10.0 °(c 0.955, $CHCl_3$); NMR ($CDCl_3$) δ: 0.92 (3H, s, CH_3), 1.3-2.6 (12H, m), 4.1-4.3 (1H, m, CH), 4.73 (1H, m, CH), 4.97 (1H, m, CH); IR (KBr): 3510, 1690 cm^{-1}; MS m/z: 194 (M^+). Anal. Calcd for $C_{12}H_{18}O_2$ C 74.19, H 9.34. Found C 74.02, H 9.53.

(-)-(4aS,7R,8aR)-7-Methylsulfonyloxy-5-methylene-8a-methyl-decahydronaphthalen-2-one (27)

To a cooled (0 °C) solution of **26** (534 mg, 2.75 mmol) in methylene chloride (15 ml) was added pyridine (0.89 ml, 11.0 mmol), methanesulfonyl chloride (0.42 ml, 5.50 mmol), and diisopropylethylamine (1.44 ml, 8.25 mmol). The mixture was stirred for 10 min and diluted with ethyl acetate. The whole was washed with 10% HCl, satd. $NaHCO_3$, and brine and dried over $MgSO_4$. Concentration and purification by silica gel column chromatography (ethyl acetate/benzene=1:2) afforded **27** (726 mg, 97%) as colorless prisms of mp 119-123 °C. $[\alpha]_D^{25}$ -24.8 °(c 1.00, $CHCl_3$); NMR ($CDCl_3$) δ: 0.91 (3H, s, CH_3), 1.4-2.9 (11H, m), 2.98 (3H, s, CH_3), 4.76 (1H, m, CH), 5.00 (1H, m, CH), 5.11 (1H, m, CH); IR ($CHCl_3$): 1705, 1650 cm^{-1}; MS m/z: Calcd for $C_{13}H_{20}O_4S$ 272.1080. Found 272.1045.

(-)-(4aS,7S,8aR)-7-(tert-Butyldimethylsilyl)oxy-5-methylene-8a-methyl-decahydronaphthalen-2-one (29)

A mixture of **27** (427 mg, 1.57 mmol), KO_2 (335 mg, 4.71 mmol), and 18-crown-6 (1.24 g, 4.71 mmol) in DMSO (8 ml) and DME (8 ml) was stirred at 0 °C for 1 h. After the addition of water (4 ml) and N-HCl (3 ml) the mixture was concentrated and diluted with CH_2Cl_2. Filtration and concentration afforded a yellow oil (3.52 g). Purification by silica gel column chromatography (benzene/ethyl acetate=2:1) afforded **30** (41.8 mg, 15%) and a mixture of **28** and dimethylsulfone (168 mg).

A solution of the above mixture of **28**, tert-butyldimethylchlorosilane (261 mg, 1.73 mmol), imidazole (118 mg, 1.73 mmol), and 4-dimethylaminopyridine (2 mg) in DMF (1 ml) was stirred at room temperature for 48 h and diluted with ethyl acetate. The whole was washed with 10% HCl, satd. $NaHCO_3$, and brine and dried over $MgSO_4$. Concentration and purification through silica gel column chromatography (benzene/ethyl acetate=100:1) afforded **29** (94 mg, 20%) as a colorless oil. $[\alpha]_D^{20}$ -28.7 °(c 1.235, $CHCl_3$); NMR ($CDCl_3$) δ: 0.06 (6H, s, CH_3 x 2), 0.66 (3H, s, CH_3), 0.84 (9H, s, t-Bu), 1.1-2.6 (11H, m), 3.68 (1H, m, CH), 4.52 (1H, m, CH), 4.84 (1H, m, CH); IR ($CHCl_3$): 1705, 1645 cm^{-1}; MS m/z: Calcd for $C_{18}H_{32}O_2Si$ 308.2170. Found 308.2170.

30: $[\alpha]_D^{25}$ +3.05 °(c 1.18, $CHCl_3$); NMR ($CDCl_3$) δ: 0.77 (3H, s, CH_3), 1.5-2.7 (9H, m), 4.9-5.0 (2H, m, $C=CH_2$), 5.70 (1H, m, CH), 6.2 (1H, m, CH); IR ($CHCl_3$): 1710, 1638, 1600 cm^{-1}; MS m/z: 176 (M^+).

(-)-(3S,4aS,7S,8aR)-Methyl 3-(7-(tert-butyldimethylsilyl)oxy-5-methylene-8a-methyl-2-oxo-decahydronaphthalen)acetate (32)

To a cooled (-78 °C) LDA (0.55 mmol) solution in THF (1 ml) was added a solution of **29** (110 mg, 0.34 mmol) in THF (0.5 ml), and the mixture was stirred for 20 min. After the addition of HMPA (0.16 ml, 0.92 mmol) a solution of methyl bromoacetate (0.065 ml, 0.69 mmol) in THF (1 ml) was added and the whole was stirred for 1 h and quenched with satd. NH_4Cl. The mixture was extracted with ether and chloroform. The combined extracts were washed with 10% HCl, satd. $NaHCO_3$, and brine and dried over $MgSO_4$. Concentration and purification through silica gel column chromatography (benzene/ethyl acetate/ether=100:1:2) afforded **32** (109 mg, 80%) as a colorless oil. $[\alpha]_D^{20}$ -60.7 °(c 1.390, $CHCl_3$); NMR ($CDCl_3$) δ: 0.06 (6H, s, CH_3 x 2), 0.74 (3H, s, CH_3), 0.90 (9H, s, t-Bu), 1.4-2.6 (11H, m), 2.92 (1H, m, CH), 3.70 (3H, s, CH_3), 3.74 (1H, m, CH), 4.58 (1H, m, CH), 4.90 (1H, m, CH); IR ($CHCl_3$): 1735, 1708, 1645 cm^{-1}; MS m/z: Calcd for $C_{17}H_{27}O_4Si$ (M^+-t-Bu) 323.1678. Found 323.1681.

(-)-(3R,4aS,7S,8aR)-Methyl 3-(7-(tert-butyldimethylsilyl)oxy-5-methylene-8a-methyl-2-oxodecahydronaphthalen)acetate (33)

A mixture of **32** (19.2 mg, 0.05 mmol) and potassium tert-butoxide (1.1 mg, 0.01 mmol) in THF (1 ml) was stirred at room temperature for 10 min and quenched with satd. NH_4Cl. The mixture was extracted with ether. The extracts were washed with brine and dried over $MgSO_4$. Concentration and purification through silica gel column chromatography (benzene/ethyl acetate=10:1) afforded **33** (14.5 mg, 76%) as a colorless oil. $[\alpha]_D^{27}$ -8.68 °(c 2.305, $CHCl_3$); NMR ($CDCl_3$) δ: 0.08 (6H, s, CH_3 x 2), 0.70 (3H, s, CH_3), 0.90 (9H, s, t-Bu), 1.2-3.0 (12H, m), 3.68 (3H, s, CH_3), 3.74 (1H, m, CH), 4.55 (1H, m, CH), 4.88 (1H, m, CH); IR ($CHCl_3$): 1730, 1710, 1645 cm^{-1}; MS m/z: Calcd for $C_{21}H_{36}O_4Si$ 380.2380. Found 380.2380.

(+)-(3aR,4aS,7S,8aR,9R)-7-(tert-Butyldimethylsilyl)oxy-dodecahydro-8a-methyl-5-methylenenaphtho[2,3-b]furan-2-one (34)

A mixture of **33** (45.0 mg, 0.118 mmol) and sodium borohydride (2.24 mg, 0.059 mmol) in methanol (2 ml) was stirred at -78 °C for 1 h and concentrated. After the addition of ether (5 ml) and 10% HCl, the mixture was stirred at 0 °C for 10 min and then diluted with ether. The mixture was washed with satd. $NaHCO_3$ and brine and dried over $MgSO_4$. Concentration and purification through silica gel column chromatography (benzene/ethyl acetate=20:1) afforded **34** (33.6 mg, 81%) as a colorless solid of mp 104-107 °C. $[\alpha]_D^{24}$ +18.6 °(c 1.450, $CHCl_3$); NMR ($CDCl_3$) δ: 0.08 (6H, s, CH_3 x 2), 0.84 (3H, s, CH_3), 0.90 (9H, s, t-Bu), 1.0-2.9 (13H, m), 3.76 (1H, m, CH), 4.54 (1H, m, CH), 4.84 (2H, m, CH); IR ($CHCl_3$): 1770, 1645 cm^{-1}; MS m/z: Calcd for $C_{20}H_{34}O_3Si$ 350.2277. Found 350.2293.

(+)-Ivalin tert-butyldimethlsilyl ether (35)

To a cooled (-78 °C) solution of LDA (0.144 mmol) in THF (0.5 ml) wa added a solution of **34** (17.9 mg, 0.048 mmol) in THF (0.5 ml) and the whole was stirred for 15 min. A formalin gas was bubbled through the above solution with a stream of nitrogen gas. The mixture was quenched with satd. NH_4Cl and diluted with ethyl acetate. The whole was washed with 10% HCl, satd. $NaHCO_3$, and brine and dried over $MgSO_4$. Concentration and purification through silica gel column chromatography (benzene/ethyl acetate=20:1) afforded the corresponding alcohol (15.7 mg, 74%) as colorless solid. This was used directly in the next step.

A solution of the solid obtained above (13.1 mg, 0.034 mmol), pyridine (0.011 ml, 0.14 mmol), methanesulfonyl chloride (0.005 ml, 0.068 mmol), and diisopropylethylamine (0.018 ml, 0.1 mmol) in methylene chloride (0.5 ml) was stirred at 0 °C for 15 min and diluted with ethyl acetate. The whole was washed with 10% HCl, satd. $NaHCO_3$, and brine, and then dried over $MgSO_4$. Concentration and purification through silica gel column chromatography (benzene/ethyl acetate=20:1) afforded **35** (6.2 mg, 50%) as colorless solid of mp 111-113 °C. $[\alpha]_D^{25}$ +95.4 °(c 0.48, $CHCl_3$); NMR ($CDCl_3$) δ: 0.07 (6H, s, CH_3 x 2), 0.83 (3H, s, CH_3), 0.89 (9H, s, t-Bu), 1.0-2.7 (9H, m), 3.00 (1H, m, CH), 3.79 (1H, m, CH), 4.46 (1H, m, CH), 4.52 (1H, m, CH), 4.86 (1H, m, CH), 5.60 (1H, m, CH), 6.15 (1H, m, CH); IR ($CHCl_3$): 1760, 1665, 1645 cm^{-1}; MS m/z: Calcd for $C_{20}H_{31}O_3Si$ (M^+-Me) 347.2040. Found 347.2022.

(+)-Ivalin (4)

A solution of **35** (3.0 mg, 0.008 mmol) in a mixture of 40% HF and acetonitrile (5:95. 0.2 ml) was stirred at room temperature for 10 min and diluted with chloroform. The whole was washed with satd. $NaHCO_3$ and brine and then dried over $MgSO_4$. Concentration and purification through silica gel column chromatography (benzene/ethyl acetate=2:1) afforded **4** (1.6 mg, 78%) as colorless plates of mp 131-134 °C (recrystallized from ether-hexane). $[\alpha]_D^{25}$ +140.0 °(c 0.16, $CHCl_3$); NMR ($CDCl_3$) δ: 0.84 (3H, s, CH_3), 1.0-2.4 (9H, m), 2.27 (1H, dd, J=1.2 and 15 Hz, CH), 3.00 (1H, m, CH), 3.82 (1H, m, CH), 4.49 (1H, m, CH), 4.56 (1H, d, J=1.4 Hz, CH), 4.89 (1H, d, J=1.4 Hz, CH), 5.61 (1H, d, J=1.1 Hz, CH), 6.15 (1H, d, J=1.1 Hz, CH); IR ($CHCl_3$): 3600, 1760, 1665, 1645 cm^{-1}; MS m/z: Calcd for $C_{15}H_{20}O_3$ 248.1410. Found 248.1388.

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16. Ratios were determined by NMR analysis of the crude aldehydes.
17. Each aldehyde (**17**, **18**) was obtained by PCC oxidation of the corresponding alcohol (**20**, **21**). ^{13}C NMR ($CDCl_3$) for trans-**17** δ: 11.0 (q), 23.5 (q), 24.7 (t), 34.6 (t), 39.5 (t), 46.2 (d), 50.8 (s), 63.9 (t), 64.6 (t), 107.9 (s), 113.8 (t), 145.3 (s), 205.0 (d). for cis-**18** δ: 22.6 (q), 23.2 (q), 25.9 (t), 35.0 (t), 46.6 (t), 48.8 (s), 52.8 (d), 64.2 (t), 64.6 (t), 108.1 (s), 113.9 (t), 145.6 (s), 207.1 (d).
18. The reaction of mesylate (**23**) with sodium cyanide was very sluggish in DMF or DMSO solvent, probably due to the neopentyl character of the alcohol group.
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