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DIASTEREOSELECTIVE 1,4-ADDITION OF VARIOUS NUCLEOPHILES TO 5-TRIMETHYLSILYL-2-CYCLOHEXENONE: SYNTHESIS OF (+)-RAMULOSIN

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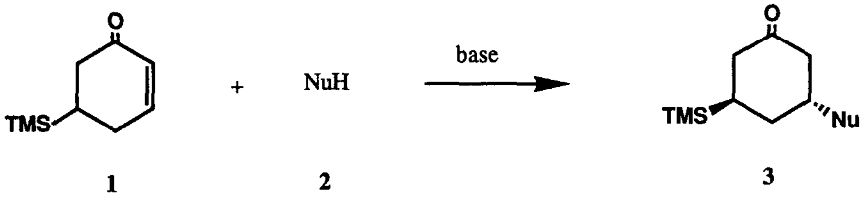
Abstract: Base catalyzed reaction of active methylene compounds or oxygen catalyzed reaction of trialkylboranes via radical pathway with 5-trimethylsilyl-2-cyclohexenone (**1**) gave the corresponding products with modest to high (3:2 - 20:1) diastereopurities. High diastereoselectivity (6:1 - >20:1) was observed in the reactions of enol silyl ethers, allylsilanes, hydrogenperoxide, and diethylaluminium cyanide with **1** and its 3-substituted derivatives. Full details of the total synthesis of (+)-ramulosin utilizing the diastereospecific product are also described.

During our efforts to utilize newly developed chiral building block 5-trimethylsilyl-2-cyclohexenone (**1**),[1)] the need for investigation on stereoselectivity in 1,4-addition of various kinds of nucleophiles to **1** emerged, since only limited extent of stereoselectivity in 1,4-addition of nucleophiles to 5-substituted 2-cyclohexenones have been studied.[2)]

In the preceding paper,[3)] we reported a highly diastereoselective Cu(I) catalyzed 1,4-addition of Grignard reagents to **1** and subsequent transformation of the adducts into several optically active terpenes. In this paper we will disclose the scope and limitation of 1,4-addition of various kinds of nucleophiles to **1**, and describe the full details of the total synthesis of (+)-ramulosin.[4)]

Our investigation was begun with the base catalyzed 1,4-addition of active methylene compounds to **1** (Scheme 1). Dimethyl malonate and methyl cyanoacetate reacted with **1** at room temperature in the presence of NaOMe to give the corresponding adducts in good yields. However, with acetylacetone, dibenzoylmethane or ethyl acetoacetate, 1,4-addition did not proceed under similar reaction conditions, and a complex mixture was obtained under forced conditions. For nitroalkanes, KF-alumina catalyzed 1,4-addition[5)] afforded the corresponding adducts in high yields. These results are listed in Table 1. The trimethylsilyl group substituted cyclohexenone derivative **1** is slightly less reactive toward these nucleophiles than the parent cyclohexenone, presumably due to the steric effect of bulky trimethylsilyl group. The trans/cis ratios of the adducts were strongly influenced by the nature of the active methylene compounds, such as acidity and bulkiness. In general, the less reactive nucleophiles showed the lower selectivity.



NuH=active methylene compound

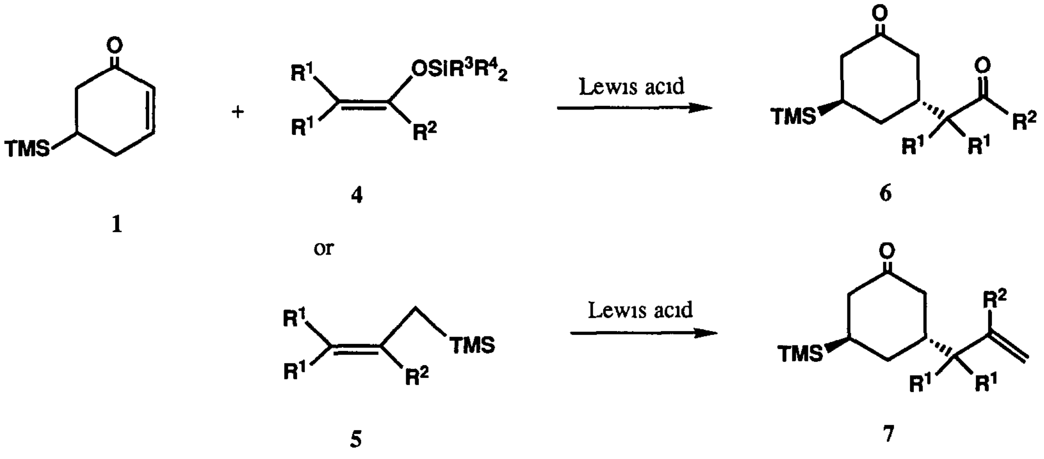
Scheme 1.

Table 1. Base catalyzed 1,4-addition of active methylene compounds to **1**

entry	reagent[a] NuH	catalyst	product 3	yield[b] %	ratio[c] trans/cis
1	$CH_2(CO_2Me)_2$	MeONa	**3a**[d]	84	10/1
2	$CH_2(CN)CO_2Me$	MeONa	**3b**[d]	81	7/3[e]
3	Me_2CHNO_2	DBU[g]	**3c**[f]	80	3/2
4		KF-alumina	**3c**	93	1/1
5	CH_3NO_2	KF-alumina	**3d**[f]	80	20/1

a) The reaction was carried out at rt. b) Isolated yield. c) The ratio was evaluated by ^{13}C NMR. d) The diastereo structure of major isomer was confirmed by the transformation into **6b**. e) The ratio was determined after demethoxycarbonylation. f) The diastereo structure was tentatively assigned. g) Diazabicycloundecene.

Above somewhat disappointing results led us to check the reactions with more reactive species, such as Lewis acid catalyzed 1,4-addition of a enol silyl ether, silyl ketene acetals, and allylsilanes[6] to **1** (Scheme 2, Table 2). In these cases, the reactions proceeded smoothly at -78 °C and the diastereoselectivity was extremely high except entry 3, in which reaction, a bulky silyl ketene acetal was used. Use of enol silyl ethers of the other ketones such as acetone and propiophenone under the same reaction conditions afforded a complex mixture.



Scheme 2.

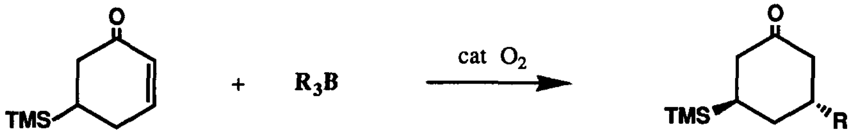
Table 2. Lewis acid catalyzed reaction of enol silyl ethers and allylsilanes

entry	reagent a) 4 or 5		catalyst	product	yield b) %	ratio c) trans/cis
1	**4a**	$CH_2{=}C(Ph)OTMS$	$SnCl_4$	**6a**f)	84	–d)
2	**4b**	$CH_2{=}C(OEt)OTBS$	$SnCl_4$	**6b**e)	95	–d)
3	**4c**	$Me_2C{=}C(OMe)OTMS$	$SnCl_4$	**6c**f)	96	6/1
4	**5a**	$CH_2{=}CH{-}CH_2TMS$	$TiCl_4$	**7a**g)	79	–d)
5	**5b**	$CH_2{=}C(Me)CH_2TMS$	$TiCl_4$	**7b**h)	79	–d)
6	**5c**	$Me_2C{=}CH{-}CH_2TMS$	$TiCl_4$	**7c**h)	79	20/1

a) The reaction was carried out at -78 °C in dry CH_2Cl_2. b) Isolated yield. c) The ratio was evaluated by ^{13}C NMR. d) cis-Isomer was not detected by ^{13}C NMR. e) The diastereo structure was confirmed by the synthesis of (+)-ramulosin. f) The diastereo structure was assigned by analogy with **6b**. g) The diastereo structure was confirmed on the hydrogenated product, 3-propyl-5-(trimethylsilyl)cyclohexanone, by the comparison with the authentic sample prepared by the 1,4-addition of PrMgBr to **1**. h) The diastereo structure was assigned by analogy with **7a**.

As an example of 1,4-addition of alkyl radicals to **1**, oxygen catalyzed 1,4-addition of trialkylborane was examined. When **1** was reacted with two equivalents of tricyclohexylborane at room temperature for 4 h by bubbling with air slowly, 1,4-adduct was obtained in 52% yield, and the trans/cis ratio was 4/1. In the case of trihexylborane, the reaction was so slow that only 28% yield of product (trans/cis=3/1) was produced after

22 h at room temperature (Scheme 3).[7)]

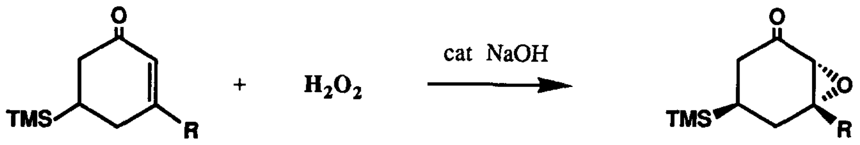


1 **8** **9**

R=c-hexyl, hexyl

Scheme 3.

Epoxidation of **1** and its 3-substituted derivatives (**10** and **11**) was also carried out (Scheme 4). Under typical reaction conditions,[8)] the reaction proceeded smoothly in a highly diastereoselective (10/1-20/1) manner to give the corresponding epoxy ketones in good yields (74-76%). Presence of a substituent at 3 position slightly contributes to the enhancement of diastereoselectivity. These results are listed in table 3.



1 R=H
10 R=Me
11 R=Et

12

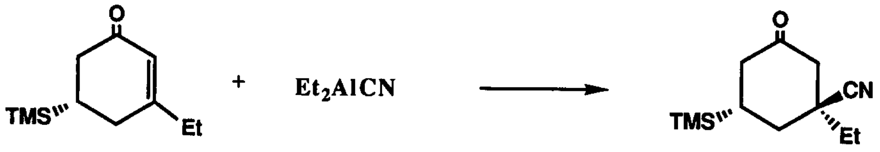
Scheme 4.

Table 3. Epoxidation of 5-trimethylsilyl-2-cyclohexenones

entry	R[a)]	product	yield/%[b)]	trans/cis[c)]
1	H	**12a**[d)]	74	10/1
2	Me	**12b**[d)]	76	20/1
3	Et	**12c**[d)]	76	20/1

a) The reaction was carried out at 0 °C. b) Isolated yield. c) The ratio was evaluated by ^{13}C NMR. d) The diastereo structure was assigned tentatively.

Hydrocyanation of (±)- and (S)-(+)-**11** with Et$_2$AlCN[9] in THF at -40 °C up to room temperature gave the corresponding 1,4-adducts as a single diastereoisomer (70-75%).[10]



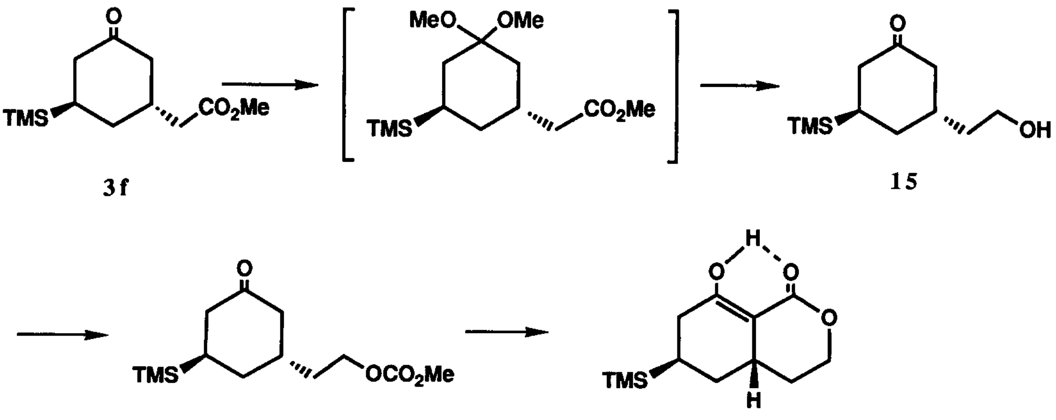
11 **13** **14**

(S)-(+)-**11** (-)-**14**

Scheme 5.

In conclusion, chirality transfer utilizing 1,3-diastereoselection of **1** by 1,4-addition of various kinds of reagents, except less reactive active methylene compounds and radical species, is a prospective way to build up a wide range of functionalized chiral cyclohexanones which should be useful intermediates for a variety of optically active molecules.

Thus the synthesis of (+)-ramulosin[4] utilizing above results was examined. As a model study, the construction of 8-hydroxy-3,4,4a,5,6,7-hexahydroisocoumarin skeleton by an intramolecular cyclization of carbonate **16** was examined (Scheme 6). The carbonate was prepared from 3-(methoxycarbonylmethyl)-5-(trimethylsilyl)cyclohexanone **3f** which was prepared by the dealkoxycarbonylation of **3a**.



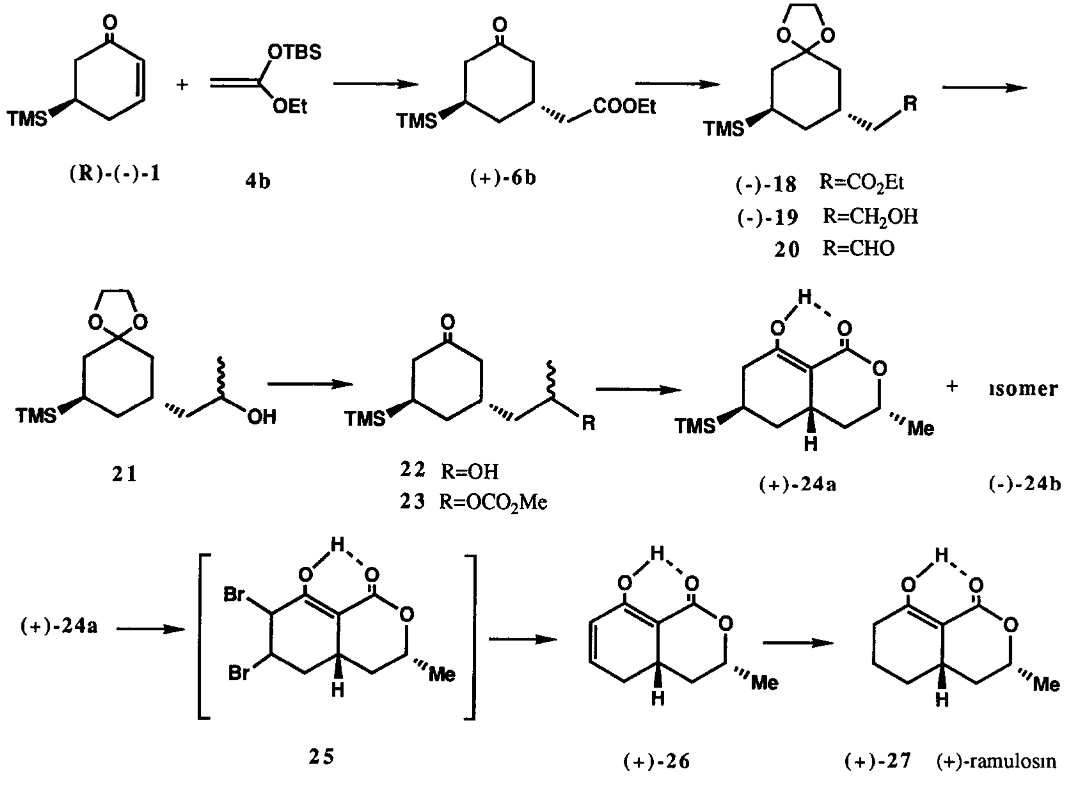
3f **15**

16 **17**

Scheme 6.

Conversion of the ester **3f** to the alcohol derivative **15** (83% overall yield) was easily achieved by the sequential treatment of **3f** with methyl orthoformate in the presence of toluenesulfonic acid, lithium aluminium hydride (LAH), and dilute hydrochloric acid. Esterification of **15** with methyl chloroformate in the presence of pyridine gave the corresponding carbonate **16** in high yield (97%). Intramolecular cyclization of the carbonate in THF solution proceeded smoothly at room temperature with freshly prepared potassium t-butoxide to give the lactone **17** in 83% yield.

On the basis of above results, the synthesis of (+)-ramulosin was carried out (Scheme 7). The reaction of (R)-(-)-**1** with the t-butyldimethylsilyl ketene acetal **4b** gave (+)-**6b** (87%) diastereoselectively, which was converted to acetal derivative (-)-**18** (82%). Reduction of (-)-**18** with DIBAH at low temperature (-78 °C or below) to the aldehyde **20** followed by the reaction with methyllithium gave the alcohol **21** in 45-56% yields, however, this method lacked reproducibility.



Scheme 7

Thus (-)-**18** was reduced to the alcohol (-)-**19** which was then oxidized with PDC in the presence of ground molecular sieves and reacted with methyllithium to give **21** in 65% overall yield. The alcohol consisted of two diastereoisomers (ca 1:1) which were chromatographically inseparable. While the use of methylaluminium reagent, MAD,¹¹⁾ in place of methyllithium did not change the ratio of diastereomers, alcohols **21** with different ratios (2:1 and 3:1) were obtained by the use of methylmagnesium iodide and (triisopropoxy)methyltitanium in 35 and 57% yields respectively. However, the major isomer was undesired one. Though the chirality inversion of **21** (3:1 mixture) was achieved by the Mitsunobu reaction, the overall yield of **21** with the desired stereochemistry was almost the same as that obtained with methyllithium. After deprotection (92%) of **21** (1:1 mixture), esterification with methyl chloroformate was carried out as described in the model study to yield the carbonate **23** in 89% yield. Intramolecular cyclization gave easily separable two diastereoisomers in 83% combined yield [(+)-**24a**, 36%, (-)-**24b**, 47%]. Bromination of (+)-**24a** with excess (2.5 equiv.) bromine gave dibromide **35** which was subsequently reduced with zinc to give (+)-**26** in 52% overall yield. Conjugate reduction of (+)-**26** by the method of Pietrusiewicz et al¹²⁾ gave (+)-ramulosin in 56% yield.

Experimental

Proton NMR spectra were taken on a Hitachi R-24B(60 MHz) and ^{13}C NMR spectra were taken on a JEOL FX-90Q. Infrared spectra were recorded on a Hitachi 260-50 spectrophotometer. Optical rotations were measured on a Horiba SEPA-200 automatic polarimeter.

3-[Bis(methoxycarbonyl)methyl]-5-(trimethylsilyl)cyclohexanone (**3a**): A solution of 5-trimethylsilyl-2-cyclohexenone (**1**, 1.00 g, 5.97 mmol), dimethyl malonate (880 mg, 6.57 mmol, 1.1 eq.), and NaOMe (0.6 mmol) in methanol (9 ml) was stirred at rt for 24 h under argon. After treatment with aq. NH_4Cl, the solution was extracted with ether. Removal of the solvent and purification by column chromatography (solvent:hexane/ether=3/1) afforded **3a** (1.51 g, 84%). Oil. ^1H NMR($CDCl_3$):δ=0.0(9H, s), 0.8-3.2(8H, m), 3.68(6H, s), 4.35(1H, d, J=10Hz). ^{13}C NMR($CDCl_3$):δ=-3.5, 21.6, 28.6, 37.6, 41.7, 44.5, 52.5, 52.5, 54.5, 168.3, 168.5, 210.6. IR(neat): 1710, 1735, and 1755 (C=O) cm^{-1}. Found: C 55.64, H 8.23%. Calcd for $C_{14}H_{24}O_5Si$: C 55.97, H 8.05%.

3-(Cyanomethyl)-5-(trimethylsilyl)cyclohexanone (**3e**): To a solution of sodium methoxide (4.0 mmol) in methanol (120 ml) were added methyl cyanoacetate (4.36 g, 44.0 mmol, 1.1 eq.) and then 5-trimethylsilyl-2-cyclohexenone (**1**, 6.72 g, 40 mmol). After stirred at rt under argon for 45 min, the reaction mixture was treated with aq NH_4Cl, and extracted with CH_2Cl_2. Removal of the solvent and purification by column chromatography on silica gel (solvent:hexane/AcOEt=4/1) afforded 3-[cyano(methoxycarbonyl)methyl]-5-(trimethylsilyl)cyclohexanone (**3b**, 8.65 g, 81%). Oil. Bp 145-165 °C/0.006 mmHg (bath temp.). ^1H NMR($CDCl_3$): δ=0.0(9H, s), 0.9-3.0(8H, m), 3.50(1H, d, J=8Hz), 3.77(3H, s). IR(KBr): 1710, 1745, and 1755 (C=O) cm^{-1}. Found: C 57.86, H 8.02, N 5.23%. Calcd for $C_{13}H_{21}O_3NSi$: C 58.39, H 7.92, N 5.24%. A solution of the cyano ester (**3b**, 8.65 g, 32.4 mmol) and lithium hydroxide monohydrate (1.5 g, 35.6

mmol) dissolved in methanol (160 ml) was stirred at rt for 16 h. Usual workup afforded crude carboxylic acid (7.74 g) which was heated over the range of 135-145 °C for 1.5 h in the presence of quinoline (0.77 g). After cooled to rt the crude product was extracted with ether, and washed with 2M HCl and saturated aq. $NaHCO_3$. Removal of solvent and purification by flash column chromatography (solvent: hexane/AcOEt=5/1) gave **3e** (3.85 g, 57%). ^{1}H NMR($CDCl_3$):δ=0.0(9H, s), 0.7-2.9(10H, m). IR(neat): 1700 (C=O) and 2240 (CN) cm^{-1}. Found: C 62.89, H 9.38, N 6.78%. Calcd for $C_{11}H_{19}ONSi$: C 63.10, H 9.15, N 6.69%. On standing in a refrigerator, the diastereomeric mixture crystallized partially. Filtration and recrystallization gave white crystals, whose diastereo structure was confirmed by the transformation into **6b**. trans-Isomer: mp 76.5-77.5 °C. ^{13}C NMR($CDCl_3$):δ=-3.7, 21.0, 21.3, 29.1, 34.9, 41.5, 45.3, 117.8, 209.9. cis-Isomer: oil. ^{13}C NMR($CDCl_3$):δ=-3.9, 24.1, 25.5, 31.4, 38.1, 41.1, 46.5, 117.4, 209.2.

3-(1-Methyl-1-nitroethyl)-5-(trimethylsilyl)cyclohexanone (**3c**): Method A: To a mixture of **1** (86 mg, 0.53 mmol) and 2-nitropropane (57.2 mg, 0.67 mmol) was added one drop of DBU. After stirred at rt for 85 min, the mixture was subjected to direct purification by tlc to give **3c** (105 mg, 80%). Method B: To a THF solution (1 ml) of **1** (168 mg, 1 mmol) and 2-nitropropane (445 mg, 5 mmol) was added KF-alumina catalyst (1.5 g), and the mixture was stirred under argon at rt for 5 h. The mixture was filtered through a short pad of celite, and the catalyst was washed with ether. Removal of the solvent and purification by tlc (solvent:hexane/ether=3/1) gave **3c** (240 mg, 93%). ^{1}H NMR ($CDCl_3$): δ=0.0(9H, s), 0.7-3.33(8H, m), 1.52(6H, s). ^{13}C NMR($CDCl_3$):δ=-3.7, -2.8, 20.3, 22.3, 22.6, 23.5, 23.7, 25.3, 25.6, 27.0, 40.1, 41.0, 41.6, 42.6, 49.6, 90.7, 91.0, 209.4, 210.3. IR(KBr): 1710 (C=O) and 1540 (NO_2) cm^{-1}. Found: C 55.62, H 9.39, N 5.41%. Calcd for $C_{12}H_{23}O_3NSi$: C 55.99, H 9.01, N 5.44%.

3-Nitromethyl-5-(trimethylsilyl)cyclohexanone (**3d**): To a solution of **1** (3.36 g, 20 mmol) and nitromethane (6.1 g, 100 mmol) dissolved in THF (20 ml) was added KF-alumina catalyst (2 g), and the mixture was stirred at rt for 7 h. Filtration of the reaction mixture through celite, washing of the catalyst with ether, removal of the solvent, and distillation of the product under reduced pressure [170-180 °C/2-3 mmHg (bath temp.)] gave **3d** (3.49 g, 76%). Mp 43-44 °C. ^{1}H NMR($CDCl_3$):δ=0.0(9H, s), 0.9-3.35(8H, m), 4.33(2H, d, J= 7Hz). ^{13}C NMR($CDCl_3$):δ=-3.6, 21.5, 27.6, 37.0, 41.7, 43.6, 75.7, 209.7. IR(neat): 1709 (C=O) and 1555 (NO_2) cm^{-1}. Found: C 52.26, H 8.52, N 6.15%. Calcd for $C_{10}H_{19}O_3NSi$: C 52.37, H 8.35, N 6.11%.

3-(2-Benzoylmethyl)-5-(trimethylsilyl)cyclohexanone (**6a**): To a cooled (-78 °C) solution of **1** (168 mg, 1 mmol) and α-trimethylsiloxystylene (210 mg, 1.1 mmol) dissolved in CH_2Cl_2 (5 ml) was added tin(IV) chloride (0.13 ml, 1.1 mmol), and the mixture was stirred at that temperature for 1.5 h. After addition of water, the reaction mixture was extracted with ether. Removal of the solvent and purification by tlc (solvent:hexane/ether=3/2) gave **6a** (243 mg, 84%). Mp 54.5-56.5 °C. ^{1}H NMR($CDCl_3$):δ=0.0(9H, s), 0.9-3.2(10H, m), 7.2-7.6(3H, m), 7.8-8.1(2H, m). ^{13}C NMR($CDCl_3$):δ=-3.6, 22.3, 30.1, 34.3, 41.5, 42.0, 46.7, 128.0, 128.6, 133.2, 137.1, 198.6, 212.3. IR(KBr): 1680 and 1700 (C=O) cm^{-1}. Found: C 70.75, H 8.47%. Calcd for $C_{17}H_{24}O_2Si$: C 70.78, H, 8.39%.

3-(Ethoxycarbonylmethyl)-5-(trimethylsilyl)cyclohexanone (**6b**): The reaction of **1** (168 mg, 1 mmol) and t-butyldimethylsilylketene acetal of ethyl acetate (405 mg, 2 mmol) in CH_2Cl_2 in the presence of tin(IV) chloride (0.23 ml, 2 mmol) was carried out at -78 °C for 10 min. Work up as mentioned above gave **6b** (242 mg, 95%). Oil. ^{1}H NMR($CDCl_3$):δ=0.0(9H, s), 0.7-3.2(10H, m), 2.21(3H, t, J=7Hz), 4.06(2H, q, J=7Hz). ^{13}C NMR($CDCl_3$):δ=-3.5, 14.3, 21.7, 29.9, 34.9, 38.1, 41.9, 46.4, 60.4, 172.0, 211.4. IR(neat): 1710 and 1730 (C=O) cm^{-1}. Found: C 60.65, H 9.31%. Calcd for $C_{13}H_{24}O_3Si$: C 60.89, H 9.43%.

3-(1-Methoxycarbonyl-1-methylethyl)-5-(trimethylsilyl)cyclohexanone (**6c**):

Oil. ^{1}H NMR(CDCl$_3$):δ=0.0(9H, s), 0.6-2.5(8H, m), 1.12(6H, s), 3.63(3H, s). ^{13}C NMR(CDCl$_3$):δ=-2.6, 21.0, 22.1, 25.8, 27.3, 40.4, 41.6, 43.1, 49.0, 51.6, 177.0, 211.6. IR(neat): 1715 and 1730 (C=O) cm^{-1}. Found: C 61.97, H 9.34%. Calcd for $C_{14}H_{26}O_3Si$: C 62.18, H 9.69%.

3-Allyl-5-(trimethylsilyl)cyclohexanone (**7a**): To a precooled (-78 °C) solution of **1** (168 mg, 1 mmol) and allyltrimethylsilane (0.24 ml, 1.5 mmol) in dry CH_2Cl_2 (5 ml) was added titanium(IV) chloride (0.17 ml, 1.2 mmol), and the resultant solution was stirred at that temperature for 5 min. After addition of water the reaction mixture was extracted with CH_2Cl_2. Removal of the solvent and purification of the residue by tlc (solvent:hexane/ether=6/1) gave **7a** (165 mg, 79%). Oil. ^{1}H NMR(CDCl$_3$): δ=0.0(9H, m), 0.8-2.7(10H, m), 4.7-5.2(2H, m), 5.3-6.0(1H, m). ^{13}C NMR(CDCl$_3$):δ=-3.9, 21.4, 29.4, 37.4, 42.0, 46.2, 116.5, 136.1, 211.8. IR(neat): 1720 (C=O) cm^{-1}. Found: C 68.27, H 10.68%. Calcd for $C_{12}H_{22}OSi$: C 68.51, H 10.54%.

3-(2-methyl-2-propenyl)-5-(trimethylsilyl)cyclohexanone (**7b**): Oil. ^{1}H NMR(CDCl$_3$):δ=0.0(9H, s), 0.6-2.8(10H, m), 1.68(3H, s), 4.62(1H, s), 4.73(1H, s). ^{13}C NMR(CDCl$_3$):δ=-3.5, 21.5, 22.0, 29.3, 35.4, 41.6, 42.1, 46.4, 112.5, 142.9, 212.2. IR(neat): 1705 (C=O) cm^{-1}. Found: C 69.58, H 10.84%. Calcd for $C_{13}H_{24}OSi$: C 69.58, H 10.78%.

3-(1,1-Dimethyl-2-propenyl)-5-(trimethylsilyl)cyclohexanone (**7c**): Oil. ^{1}H NMR(CDCl$_3$):δ=0.0(9H, s), 0.6-3.0(8H, m), 0.98(6H, s), 4.5-5.2(2H, m), 5.3-6.1(1H, m). ^{13}C NMR(CDCl$_3$):δ=-2.6, 20.9, 24.1, 25.7, 39.2, 40.4, 41.8, 43.7, 112.1, 146.0, 213.2. IR(neat): 1707 (C=O) cm^{-1}. Found: C 70.28, H 10.91%. Calcd for $C_{14}H_{26}OSi$: C 70.52, H 10.99%.

2,3-Epoxy-5-(trimethylsilyl)cyclohexanone (**12a**): To a cooled (0 °C) solution of **1** (168 mg, 1 mmol) in methanol (1 ml) were added 35% hydrogenperoxide (0.13 ml) and aq. 6M NaOH (0.085 ml), and the mixture was stirred at that temperature for 5 min. After addition of aq. $NaHCO_3$ and $Na_2S_2O_3$, the reaction mixture was extracted with ether. Purification of the product by tlc (solvent: hexane/ether=9/1) gave **12a** (135 mg, 73%). Oil. ^{1}H NMR(CDCl$_3$):δ=0.0(9H, s), 0.7-2.2(5H, m), 3.18(1H, d, J=4Hz), 3.56(1H, t, J=3Hz). ^{13}C NMR(CDCl$_3$):δ=-3.9, 12.7, 24.3, 37.4, 54.8, 62.1, 205.3. IR(neat): 1700 (C=O) cm^{-1}. Found: C 58.32, H 9.13%. Calcd for $C_9H_{16}O_2Si$: C 58.65, H 8.75%.

2,3-Epoxy-3-methyl-5-(trimethylsilyl)cyclohexanone (**12b**): Oil. ^{1}H NMR(CDCl$_3$):δ=0.0(9H, s), 0.8-2.6(5H, m), 1.42(3H, s), 3.00(1H, s). ^{13}C NMR(CDCl$_3$):δ=-3.8, 14.4, 21.8, 29.9, 36.8, 61.4, 61.6, 206.1. IR(neat): 1700 (C=O) cm^{-1}. Found: C 60.24, H 9.59%. Calcd for $C_{10}H_{18}O_2Si$: C 60.56, H 9.15%.

2,3-Epoxy-3-ethyl-5-(trimethylsilyl)cyclohexanone (**12c**): Oil. ^{1}H NMR(CDCl$_3$):δ=0.0(9H, s), 0.8-3.4(7H, m), 0.94(3H, t, J=7Hz), 3.56(1H, s). ^{13}C NMR(CDCl$_3$):δ=-3.7, 8.7, 14.0, 27.7, 28.4, 37.1, 60.5, 65.1, 207.0. IR(neat): 1700 (C=O) cm^{-1}. Found: C 62.12, H 9.86%. Calcd for $C_{11}H_{20}O_2Si$: C 62.21, H 9.49%.

3-Cyano-3-ethyl-5-(trimethylsilyl)cyclohexanone (**14**): To a cooled (-40 °C) solution of 3-ethyl-5-trimethylsilyl-2-cyclohexenone (980 mg, 5 mmol) dissolved in THF (15 ml) was added a solution of Et_2AlCN in toluene (7 ml, 7 mmol), and the solution was allowed to warm to 0 °C over a period of 6.5 h. Chlorotrimethylsilane (1.65 ml, 13 mmol) and pyridine (1.5 ml) were added to the reaction mixture, and the resultant solution was left to warm to rt overnight. After dilution with dry pentane, the mixture was poured into ice cold aq. NH_4Cl and extracted with ether. After removal of solvent, the residue was dissolved in acetone (20 ml), and treated with water (0.5 ml) and 2 drops of 2M HCl at rt for 5 min. Removal of volatiles under vacuum and purification by flash column chromatography (solvent: hexane/AcOEt=8/1) gave **14** which was diastereomerically pure but contaminated with a small amount of unidentified by-product. Recrystallization from pentane gave pure **14** (70-75%). (±)-**14**: mp 61-2 °C. (-)-**14**: mp 66-66.5 °C, $[\alpha]_D^{27}$-80.0°(c 1.00, CHCl$_3$). ^{1}H NMR(CDCl$_3$): δ=0.06(9H, s), 1.09(3H, t, J=7Hz), 0.9-2.96(9H, m). ^{13}C NMR(CDCl$_3$):δ=

-3.79, 8.88, 23.19, 33.64, 35.43, 41.23, 45.40, 49.24, 121.73, 206.62. IR(KBr): 1715 (C=O) and 2230 (CN) cm^{-1}. Found: C 64.66, H 9.45, N 6.43%. Calcd for $C_{12}H_{21}NOSi$: C 64.52, H 9.48, N 6.27%.

3-(2-Hydroxyethyl)-5-(trimethylsilyl)cyclohexanone (**15**): To a mixture of **3f** (257 mg, 1.07 mmol) and methyl orthoformate (1 ml) in methanol (5 ml) was added a catalytic amount of p-toluenesulfonic acid. After stirred at rt for 0.5 h, the reaction was quenched with aq. $NaHCO_3$. After usual work up, the crude product was dissolved in dry THF (5 ml) and added to a suspension of LAH (80 mg) in dry THF (5 ml) at 0 °C. Usual work up followed by purification by tlc (solvent:hexane/ether=2/1) gave **15** (191 mg, 83%). Oil. ^{1}H NMR($CDCl_3$):δ=0.0(9H, s), 0.8-2.1(11H, m), 3.60(2H, t, J=6Hz). IR(neat): 1702 (C=O) and 3050-3650 (OH) cm^{-1}. Found: C 61.47, H 10.66%. Calcd for $C_{11}H_{22}O_2Si$: C 61.63, H 10.34%.

3-(2-Methoxycarbonyloxyethyl)-5-(trimethylsilyl)cyclohexanone (**16**): To a cooled (0 °C) mixture of **15** (228 mg, 1.07 mmol) and pyridine (0.26 ml, 3.2 mmol) in dry CH_2Cl_2 (5 ml), was added methyl chloroformate (0.25 ml, 3.2 mmol) and the reaction mixture was stirred at that temperature for 20 min. Addition of water, extraction with CH_2Cl_2, removal of solvent, and purification by tlc (solvent:hexane/ether=8/1) gave **16** (282 mg, 97%). Oil, bp 140-150 °C/0.06 mmHg (bath temp.). ^{1}H NMR($CDCl_3$):δ=0.0(9H, s), 0.6-2.7(10H, m), 3.71(3H, s), 4.11(2H, t, J=6Hz). IR(neat): 1705 and 1750 (C=O) cm^{-1}. Found: C 57.04, H 9.00%. Calcd for $C_{13}H_{24}O_4Si$: C 57.32, H 8.88%.

8-Hydroxy-6-trimethylsilyl-3,4,4a,5,6,7-hexahydroisocoumarin (**17**): To a freshly prepared t-BuOK (2.25 g, 30 mmol) in dry THF (50 ml), was added a solution of **16** (2.43 g, 8.93 mmol) in THF (5 ml) at rt and the reaction mixture was stirred at rt for 5 min. After addition of 2M HCl, usual work up followed by purification by flash column chromatography (solvent:hexane/AcOEt=10/1) gave **17** (1.78 g, 83%). Mp 106.5-108 °C (MeOH). ^{1}H NMR($CDCl_3$):δ=0.0(9H, s), 0.7-2.9(8H, m), 4.1-4.6(2H, m). IR(KBr): 1640 (C=O) and 1615 (C=C) cm^{-1}. Found: C 59.89, H 8.58%. Calcd for $C_{12}H_{20}O_3Si$: C 59.96, H 8.39%.

(+)-3-(Ethoxycarbonylmethyl)-5-(trimethylsilyl)cyclohexanone [**(+)-6b**]: Preparation of **(+)-6** from **(R)-(-)-1** and **4b** was carried out as described for **6b**. Yield 87%. $[\alpha]_D^{20}$+72.8°(c 1.76, $CHCl_3$).

(-)-3-(Ethoxycarbonylmethyl)-5-(trimethylsilyl)cyclohexanone ethylene acetal [**(-)-18**]: A mixture of **(+)-6b** (16.8 g, 65.6 mmol), ethylene glycol (8.12 g, 2 equiv.), and pyridinium p-toluenesulfonate (200 mg) dissolved in toluene was heated under reflux for 1.5 h with removal of water. Usual work up followed by purification by tlc (solvent: hexane/ether=9/1) afforded **(-)-18** (16.1 g, 82%). Oil, bp 130-140 °C/0.035 mmHg (bath temp.). $[\alpha]_D^{21}$-22.28°(c 2.97, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ=0.0(9H, s), 0.5-2.8(10H, m), 1.29(3H, t, J=7Hz), 3.41(4H, s), 4.11(2H, q, J=7Hz). IR(neat): 1730 (C=O) cm^{-1}. Found: C 59.92, H 9.57%. Calcd for $C_{15}H_{28}O_4Si$: C 59.96, H 9.39%.

(-)-3-(2-Hydroxyethyl)-5-(trimethylsilyl)cyclohexanone ethylene acetal [**(-)-19**]: To a solution of **(-)-18** (300 mg, 1 mmol) in dry THF (10 ml) was added lithium aluminium hydride (60 mg) in a small portion at 0 °C, and the mixture was stirred at that temperature for 30 min. Careful addition of water and dilute HCl followed by extraction with CH_2Cl_2, removal of solvent, and purification of the residue by column chromatography (solvent: hexane/AcOEt=7/3) gave **(-)-19** (235 mg, 91%). Oil, $[\alpha]_D^{22}$-17.83°(c 2.03, $CHCl_3$). ^{1}H NMR($CDCl_3$):δ=0.0(9H, s), 0.7-2.4(10H, m), 2.76(1H, s), 3.62(2H, t, J=6Hz), 3.91(4H, s). IR(neat): 3050-3600 (OH) cm^{-1}. Found 60.66, H 10.40%. Calcd for $C_{13}H_{26}O_3Si$: C 60.42, H 10.14%.

(-)-3-(2-Hydroxypropyl)-5-(trimethylsilyl)cyclohexanone ethylene acetal (**21**): To a solution of **(-)-19** (5.77g, 22.4 mmol) in dry CH_2Cl_2 (50 ml) were added ground molecular sieves (10 g) and pyridinium dichromate (25.3 g, 67.2 mmol), and the mixture was stirred at rt for 2 h. After addition of dry ether, the mixture was filtered through a short pad of silica gel. Removal of the solvent afforded crude aldehyde (**20**, 4.54 g), which was reacted with methyllithium (21.2 mmol) in THF (50 ml) at -78 °C for 5 min. Usual workup and purification by flash column chromatography (solvent: hexane/ AcOEt=7/3) gave **21** (4.10 g, 67%). Oil. ^{1}H NMR($CDCl_3$):δ=0.0(9H, s), 0.6-2.5(11H, m), 1.26(3H, d, J=6Hz), 3.5-4.4(1H, m), 3.95(4H, s). IR(neat): 3050-3650 (OH) cm^{-1}. Found: C 61.48, H 10.41%. Calcd for $C_{14}H_{28}O_3Si$: C 61.72, H 10.36%.

(+)-3-(2-Hydroxypropyl)-5-(trimethylsilyl)cyclohexanone (**22**): To a solution of **21** (3.47 g, 12.8 mmol) in acetone were added three drops of water and TsOH (10 mg), and the reaction mixture was left at rt for 12 h. Addition of saturated aq. $NaHCO_3$, extraction with CH_2Cl_2, removal of solvent, and purification by tlc (solvent: hexane/AcOEt=3/1) gave **22** (2.69 g, 92%). Oil, bp 160-170 °C/0.05 mmHg (bath temp.). ^{1}H NMR($CDCl_3$):δ= 0.0(9H, s), 0.9-2.8(11H, m), 1.16(3H, d, J=6Hz), 3.5-4.3(1H, m). IR(neat): 1702 (C=O) cm^{-1}.

(+)-3-(2-Methoxycarbonyloxypropyl)-5-(trimethylsilyl)cyclohexanone (**23**): To a cooled (0 °C) solution of **22** (2.11 g, 9.25 mmol) and pyridine (2.23 ml, 28 mmol) in CH_2Cl_2 (50 ml) was added methyl chloroformate (2.17 ml, 28 mmol), and the solution was stirred at that temperature for 0.5 h. Then the same amount of pyridine and methyl chloroformate were added, and the mixture was stirred for 1 h (0 °C). Usual work up and purification by flash column chromatography (solvent: hexane/AcOEt=8/1) gave **23** (2.37 g, 89%). Oil, bp 160-170 °C/0.05 mmHg (bath temp.). ^{1}H NMR($CDCl_3$):δ=0.0(9H, s), 0.9-3.0(10H, m), 1.25(3H, d, J=6Hz), 3,29(3H, s), 4.4-5.0(1H, m). IR(neat): 1703 and 1740 (C=O) cm^{-1}. Found: C 58.69, H 9.29%. Calcd for $C_{14}H_{26}O_4Si$: C 58.70, H 9.15%.

(+)-8-Hydroxy-3-methyl-6-trimethylsilyl-3,4,4a,5,6,7-hexahydroisocoumarin [**(+)-24a**] and (-)-8-hydroxy-3-methyl-6-trimethylsilyl-3,4,4a,5,6,7-hexahydroisocoumarin [**(-)-24b**]: To a solution of freshly prepared t-BuOK (5.8 g, 78 mmol) in THF (50 ml) was added **23** (2.33 g, 8.15 mmol) in THF (10 ml), and the reaction mixture was stirred at rt for 1 h. Acidification with 2M HCl, extraction with CH_2Cl_2, evaporation of solvent, and purification by flash column chromatography (solvent: hexane/AcOEt=8/1) gave **(+)-24a** (746 mg, 36%) and **(-)-24b** (972 mg, 47%). **(+)-24a**: mp 87-88 °C (pentane), $[\alpha]_D^{20}$+66.74°(c 2.69, $CHCl_3$). ^{1}H NMR($CDCl_3$):δ=0.03(9H, s), 0.9-2.8(8H, m), 1.34(3H, d, J=6Hz), 4.0-4.7(1H, m), 13.05(1H, s). IR(KBr): 1605 and 1635 (C=O) cm^{-1}. Found: C 61.44, H 8.89%. Calcd for $C_{13}H_{22}O_3Si$: C 61.38, H 8.72%. **(-)-24b**: mp 45.0-45.5 °C (methanol), $[\alpha]_D^{20}$-13.78°(c 1.93, $CHCl_3$). ^{1}H NMR($CDCl_3$): δ=0.05(9H, s), 0.8-3.0(8H, m), 1.32(3H, d, J=6Hz), 4.2-4.9(1H, m), 13.04(1H, s). Found: C 61.34, H 8.86%. Calcd for $C_{13}H_{22}O_3Si$: C 61.38, H 8.72%.

(+)-8-Hydroxy-3-methyl-3,4,4a,5-tetrahydroisocoumarin [**(+)-26**]: To a solution of **(+)-24a** (167 mg, 0.657 mmol) in CCl_4 (5 ml) was added bromine (1.6 mmol) in CCl_4, and the solution was stirred at rt for 10 min. After addition of saturated $NaHCO_3$ and $Na_2S_2O_3$ solution, the reaction mixture was extracted with CH_2Cl_2. Removal of the solvent gave the crude dibromide, which was dissolved in ethanol (5 ml) and reduced with zinc (130 mg) under refluxing conditions (15 min.). The reaction mixture was filtered through celite, and the filtrate was concentrated. Purification of the crude product by flash column chromatography (solvent: hexane/AcOEt=4/1) gave **(+)-26** (62 mg, 52 %). Mp 82-83.5 °C, $[\alpha]_D^{21}$+115.54°(c 1.67, $CHCl_3$). ^{1}H NMR($CDCl_3$):δ=0.7-4.3(5H, m), 1.40(3H, d, J=6Hz), 4.1-4.8(1H, m), 6.05(1H, dd, J=2 and 10Hz), 6.2-6.7(1H, m), 12.84(1H, s). IR(KBr): 1576 and 1643 (C=O) cm^{-1}. Found: C 66.67, H 6.59%. Calcd for $C_{11}H_{12}O_3$: C 66.65, H 6.71%.

(+)-Ramulosin [**(+)-27**]: Reduction of **(+)-26** (64 mg, 0.36 mmol) was carried out by the method of Pietrusiewicz[12)] to give (+)-ramulosin in 56% yield. Mp 117.5-118.5 °C (pentane), $[\alpha]_D^{22}$+17.14°(c 0.56, EtOH), lit.[4)] mp 118-119 °C, $[\alpha]_D^{22}$+18.3°(c 1.20, EtOH). ^{1}H NMR($CDCl_3$):δ=0.6-3.0(9H, m), 1.38(3H, d, J=4Hz), 4.1-4.9(1H, m), 13,20(1H, s). IR(KBr): 1620 and 1640 (C=O) cm^{-1}. Found: C 65.75, H 7.77%. Calcd for $C_{10}H_{14}O_3$: C 65.92, H 7.75%.

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