Stereoselective Synthesis of (−)-Pinidinone

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A simple and efficient stereoselective linear approach to the total synthesis of (−)-pinidinone has been accomplished starting from propane-1,3-diol, and employing *Maruoka* asymmetric allylation and *Grubbs*' olefin cross-metathesis as the key steps.

Introduction. – N-Containing heterocyclic compounds are widespread in medicinal chemistry due to the fact that many natural and synthetic biologically active compounds share this common architectural feature. Many of the alkaloids possess potent and therapeutically interesting biological activities, which has led to their use as drug candidates or as lead compounds in drug discovery [1]. Among them, 6-alkyl-2-methylpiperidine alkaloids are prominent examples that have extensively been used as building blocks for the synthesis of biologically active natural products [2]. In fact, the natural alkaloids, structurally related to 2,6-disubstituted piperidines, have different biosynthetic origins, and the stereogenic center adjacent to the N-atom can have different configurations. Representative examples are (−)-pinidinone (**1**), dihydropinidine (**2**), isosolenopsins **3**, and structurally related *cis*-6-alkylpipecolic acids (**4**; *Fig.*).

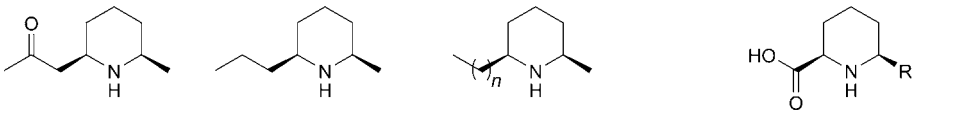


Figure. *Some naturally occurring 2,6-disubstituted piperidine alkaloids*

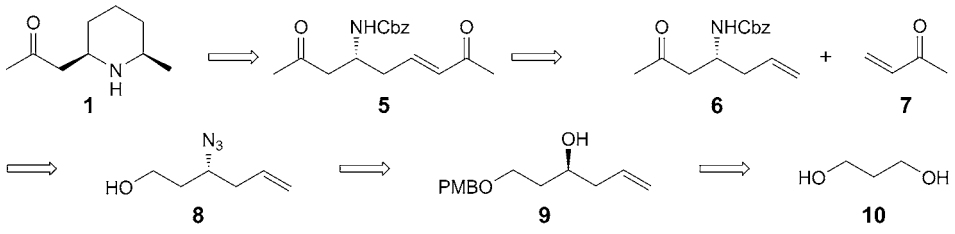
In this class, (−)-pinidinone (**1**) that contains a 2,6-disubstituted piperidine skeleton and was isolated from the needles of the Colorado blue spruce (*Picea pungens* ENGELM.) was also found in the hemolymph of the Australian mealybug (*Cryptolaemus montrouzieri* MULSANT), as well as the Mexican bean beetle (*Epilachna varivestis* MULSANT) [3]. It was reported that (−)-pinidinone (**1**) serves as defensive alkaloid because of its potent antifeedant activity against worms (*Picea*), ants, and spiders (beetles) [4a]. Due to its biological importance and scarce availability from natural sources, much effort has been devoted to the development of general methodologies and diverse approaches for its synthesis. In this context, during the past few years, three

syntheses of (−)-pinidinone were published [4a–4c], as well as the synthesis of its enantiomer (+)-pinidinone [4d]. Despite reported methods, new general, efficient, and scalable methods to access the target compounds are still highly desirable to expand the synthetic utility of these versatile building blocks.

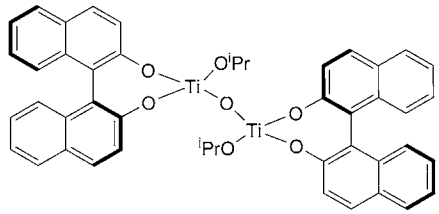
Among the various possible methods that allow the formation of a piperidine ring, the intramolecular nucleophilic displacement of an activated alcohol moiety (*e.g.*, tosylate, mesylate, or triflate) by an amine group is one of the most useful and reliable ones [5]. During the past ten years, the ring-closing metathesis (RCM) reaction has emerged as one of the most powerful synthetic tools in organic synthesis for the preparation of both carbo- and heterocyclic ring systems [6]. It is primarily due to the ready availability of many metathetic catalysts such as *Grubbs*' first- [7] and second-generation catalyst [8], *Hoveyda*'s catalyst [9], *etc.*, and also due to their high level of functional group tolerance. Furthermore, piperidine rings can also be constructed from allylamines, using either chiral pool-derived cyclization precursors or stereoselective C–N-bond formation such as azidization reaction, followed by the reduction of alcohols of the appropriate configuration.

Our retrosynthetic analysis of **1** is outlined in *Scheme 1*. As indicated, the piperidine framework could be constructed by reductive cyclization of **5**. We then anticipated that the olefin cross-metathesis precursors **6** and **7** would be potential and versatile intermediates, which can be accessed from propane-1,3-diol in a three-step sequence. The stereogenic centers C(2) and C(6) in **1** could be controlled through enantioselective allylations of aldehydes. More importantly, we have successfully implemented a strategy that minimizes protecting-group manipulation in a unique fashion, a common and unavoidable practice in (−)-pinidinone (**1**) synthesis.

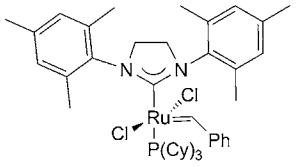
Scheme 1



Results and Discussion. – In our work directed towards the expedient synthesis of polysubstituted piperidines starting from cheap and readily available starting materials, we have recently shown that asymmetric *Marouka* allylation of aldehydes by the binol complexes (*R*,*R*)-**I** or (*S*,*S*)-**I**, one-pot reductive amination, followed by the diastereoselective cyclization, appear to be the method of choice for obtaining amines of high enantiomeric excess [10]. With these considerations, as well as in continuation of our interest in the synthesis of bioactive alkaloids, herein, we report the stereoselective synthesis of (−)-pinidinone utilizing the *Marouka* allylation in combination with *Grubbs*' cross-metathesis as key reaction sequence.



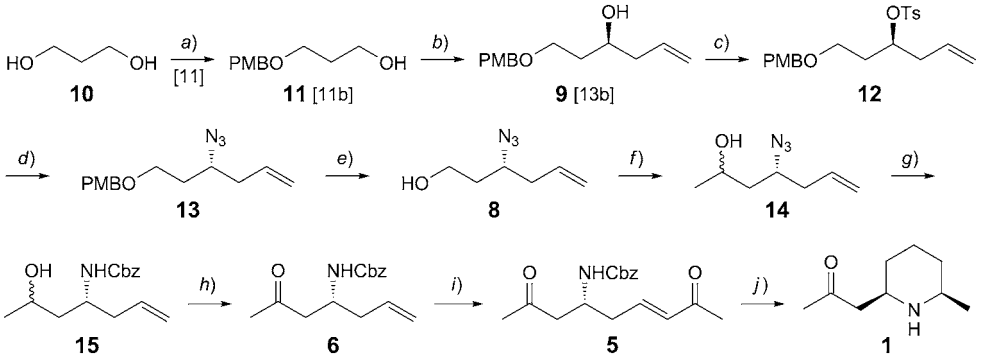
Binol complex (*S*,*S*)-**I**



Grubbs' catalyst (2nd generation)

Our synthetic endeavours commenced with selective protection of propane-1,3-diol (**10**) as 4-methoxybenzyl (PMB) ether using PMB-Br and NaH in dry THF to give **11** [11] in 95% yield (*Scheme 2*). *O*-Iodoxybenzoic acid [12] oxidation of **11**, followed by an enantioselective *Maruoka* allylation using titanium complex (*S*,*S*)-**I** and allyl(tributyl)tin furnished the homoallylic alcohol **9** [10c][13] in 84% yield with excellent enantioselectivity of 98% ee (determined by chiral HPLC)[1]). The resulting homoallylic alcohol was orthogonally protected as its tosyl ester **12** with TsCl in pyridine/CH_2Cl_2 1:1 in 92% yield [14]. The treatment of **12** with NaN_3 in DMF at 70° [14] afforded azido compound **13** in excellent yield. Then, oxidative removal [15] of the PMB group by using DDQ in CH_2Cl_2/H_2O 9:1 provided the primary alcohol **8** in 90% yield. Subsequent oxidation of **8** by *Dess–Martin* periodinane [16] in CH_2Cl_2 gave an aldehyde in quantitative yield, which was further treated with MeMgI [17] in Et_2O to afford the secondary alcohol **14** as 1:1 diastereoisomer mixture in 85% yield.

Scheme 2



a) NaH, 4-Methoxybenzyl bromide, $Bu_4N^+I^-$, THF, 0° – r.t., 5 h; 95%. *b*) *i*) *O*-Iodoxybenzoic acid, DMSO, THF, r.t., 3 h; *ii*) (*S*,*S*)-**I** (10 mol-%), $Bu_3SnCH_2CH{=}CH_2$, CH_2Cl_2, −15° – to 0°, 24 h; 84%. *c*) TsCl, Pyridine/CH_2Cl_2 1:1, 0° – r.t., 6 h; 92%. *d*) NaN_3, DMF, 70°, 3 h; 79%. *e*) DDQ (=2,3-Dichloro-5,6-dicyano-1,4-benzoquinone), CH_2Cl_2/H_2O 9:1, 0° – r.t., 1 h; 90%. *f*) *i*) *Dess–Martin* periodinane, CH_2Cl_2, 0°, 2 h; *ii*) MeMgI, Et_2O, 0° – r.t., 30 min; 85%. *g*) $LiAlH_4$, THF, 0° – r.t., 1 h then sat. $NaHCO_3$, Cbz-Cl (=benzyloxycarbonyl chloride), 90%. *h*) *Dess–Martin* periodinane, CH_2Cl_2, 0°, 1 h; 90%. *i*) Methyl vinyl ketone (**7**), *Grubbs*' second generation catalyst (5 mol-%), CH_2Cl_2, 40°, 1 h; 90%. *j*) Pd/C (10%), H_2 (ballon), AcOEt, 12 h; 72%.

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[1]) The enantioselectivity was determined by HPLC (*Waters Atlantis* dC_{18}; 150 × 4.6 mm, 5 μm, 220 nm; eluent, MeCN/H_2O 7:3, 10 ml injection volume; flow rate, 1 ml/min; t_R 6.012 min).

Reduction of the azide function in **14** using $LiAlH_4$ in dry THF to give the amine [18], followed by addition of saturated aqueous $NaHCO_3$ and Cbz-Cl afforded the Cbz-protected amine **15** in 90% yield. Then, the oxidation of the secondary alcohol with *Dess–Martin* periodinane provided the oxo derivative **6** in 90% yield.

Having successfully accomplished the synthesis of intermediate **6**, we then shifted our focus to conjunction of precursors **6** with methyl vinyl ketone (**7**) *via* olefin cross-metathesis reaction. Thus, we submitted **6** and **7** to 10 mol-% of *Grubbs*' second-generation catalyst in refluxing CH_2Cl_2 [19]. As anticipated, the reaction proceeded smoothly to afford **5** in excellent yield as a colorless crystalline solid. As premediated, the cross-metathesis product **5** was subjected to the one-pot reductive amination, followed by diastereoselective cyclization [20] using Pd/C (10%) to afford (−)-pinidinone (**1**) in good yield. The latter was isolated and characterized as a yellow oil. All the intermediate compounds including the (−)-pinidinone (**1**) were fully characterized by means of IR, ^{1}H- and ^{13}C-NMR, and mass spectral data. Furthermore, chiroptical data obtained were in complete agreement with the data reported in literature [4a–4c] (see *Exper. Part*).

Conclusions. – we have developed an efficient stereoselective protocol for the synthesis of (−)-pinidinone (**1**) by employing *Maruoka* asymmetric allylation, *Grubbs*' cross-metathesis reaction, and reductive cyclization as the key reaction steps. The presented synthetic method could be of value in the development of novel 2,6-disubstituted piperidine-based analogues.

The authors gratefully acknowledge keen interest shown by Dr. *J. S. Yadav*, Director, IICT, Hyderabad. *T. V. K.* and *G. V. R.* thank *CSIR* and *UGC*, New Delhi for financial support.

Experimental Part

General. All the reagents and solvents were reagent-grade and used without further purification unless specified otherwise. Technical-grade AcOEt and hexanes used for column chromatography (CC) were distilled prior to use. All the reactions were performed under N_2 in flame-dried or oven-dried glassware with magnetic stirring. The progress of the reactions was monitored by anal. TLC performed on *Merck* SiO_2 *60* F_{254} plates. Flash column chromatography (FC): silica gel (SiO_2; 60–120 mesh, unless stated otherwise) packed in glass columns. M.p.: *Büchi B-545*; uncorrected. Optical rotation: *JASCO DIP 300* digital polarimeter at 25° in $CHCl_3$ or MeOH. FT-IR Spectra: *Nexus* FT-IR spectrometer; in KBr or neat; $\tilde{\nu}$ in cm^{-1}. ^{1}H- and ^{13}C-NMR spectra: *Bruker* spectrometers, at 300 or 75 MHz, resp., in $CDCl_3$ solvent; δ in ppm rel. to Me_4Si as internal standard, J in Hz. LR- and HR-MS: *JEOL LCmate* mass spectrometer; in m/z.

3-[(4-Methoxybenzyl)oxy]propan-1-ol (**11**) [11b]. To a suspension of NaH (1.21 g, 52.6 mmol) in THF (20 ml) was added dropwise *propane-1,3-diol* (**10**; 2 g, 26.3 mmol) at 0° under inert atmosphere. After 1 h, $Bu_4N^+I^-$ (cat. amount) was added, followed by the addition of 4-methoxybenzyl bromide (PMB-Br; 5.76 g, 28.9 mmol). The mixture was further stirred for 4 h at r.t. After completion (of the reaction TLC), the mixture was diluted with H_2O and extracted with AcOEt (3 × 20 ml). The combined org. layers were separated, washed with brine, and dried (Na_2SO_4). The solvent was evaporated to dryness to afford crude product, which was purified by FC (SiO_2 (100–200 mesh); hexane/AcOEt 7:3) to give **11** (5.3 g, 95%). Colorless liquid. IR (KBr): 3407, 2937, 2864, 1610, 1513, 1248, 1088, 820, 772. ^{1}H-NMR: 7.20 (d, J = 8.8, 2 H); 6.82 (d, J = 7.9, 2 H); 4.42 (s, 2 H); 3.7 (s, 3 H); 3.72 (t, J = 10.8, 2 H); 3.60 (t, J = 11.8, 2 H); 1.84–1.79 (m, 2 H). ^{13}C-NMR: 159.2; 129.9; 129.3; 113.8; 72.7; 68.3; 61.1; 55.0; 32.0. ESI-MS: 219 ($[M+Na]^+$).

(3S)-1-[(4-Methoxybenzyl)oxy]hex-5-en-3-ol (**9**) [13b]. *i*) To a stirred soln. of *O*-iodoxybenzoic acid (8.6 g, 30.6 mmol) in dry DMSO (8 ml) was added a soln. of **11** (3 g, 13.1 mmol) in dry THF (50 ml) at r.t., and the mixture was stirred for 30 min. The reaction was quenched with Et_2O (5 ml), and the mixture was extracted with Et_2O (3×20 ml). The org. layer was separated, washed with aq. sat. $NaHCO_3$, and dried (Na_2SO_4). The solvent was removed under vacuum. The crude product was purified by FC (SiO_2; hexane/AcOEt 9:1) to give a yellow liquid in 90% yield (2.96 g), which was used for the next step without purification.

ii) To a stirred soln. of 1M $TiCl_4$ in CH_2Cl_2 (0.76 ml, 0.76 mmol) in CH_2Cl_2 (20 ml) was added dried $(^iPrO)_4Ti$ (0.67 ml, 2.28 mmol) at 0° under N_2. The soln. was allowed to warm to r.t. After 1 h, Ag_2O (353 mg, 1.52 mmol) was added at r.t., and the mixture was stirred for 5 h under exclusion of direct light. The mixture was diluted with CH_2Cl_2 (10 ml) and treated with (*S*)-binaphthol (872 mg, 3.05 mmol) at r.t. for 2 h to furnish chiral bis-Ti^{IV} oxide (*S,S*)-**I**. The *in situ* generated (*S,S*)-**I** was cooled to −20° and treated sequentially with above aldehyde (2.96 g, 15.2 mmol) and allyl(tributyl)tin (5.14 ml, 16.78 mmol) at −20°. The mixture was stirred for 30 min and then placed into freezer (−20°) for 18 h. The mixture was allowed to warm to 0°, the reaction was quenched with aq. sat. $NaHCO_3$ (5 ml), and the mixture extracted with CH_2Cl_2 (2×20). The solvent was evaporated to dryness to afford crude product, which was purified by FC (SiO_2; hexane/AcOEt 8:2) to give **9** (84%). Pale-yellow liquid. The enantiomeric purity of the product was determined to be 98% ee by anal. HPLC analysis. $[\alpha]_D^{25} = -5.9$ ($c = 1.0$, $CHCl_3$).

(3S)-1-[(4-Methoxybenzyl)oxy]hex-5-en-3-yl 4-Methylbenzenesulfonate (**12**). To a stirred soln. of **9** (2 g, 8.47 mmol) in dry CH_2Cl_2 and pyridine 1:1 (20 ml) at 0° was added TsCl (2 equiv., 3.2 g, 16.9 mmol). The mixture was stirred for 12 h at r.t. The reaction was quenched with aq. sat. $CuSO_4$ (5 ml), and the mixture was diluted with H_2O, and the org. layer was extracted with CH_2Cl_2 (3×10 ml). The solvent was removed under vacuum. The crude product was purified by FC (SiO_2; hexane/AcOEt 8:2) to give **12** (92%). Yellow liquid. $[\alpha]_D^{25} = +12$ ($c = 1.0$, $CHCl_3$). IR (KBr): 2923, 2854, 1611, 1513, 1360, 1247, 1175, 1095, 817. ^{1}H-NMR: 7.76 (*d*, $J = 8.3$, 1 H); 7.31–7.14 (*m*, 5 H); 6.83 (*m*, 3 H); 5.71–5.55 (*m*, 1 H); 5.01 (*m*, 1 H); 4.83–4.75 (*m*, 1 H); 4.43 (*s*, 2 H); 3.79 (*s*, 3 H); 3.74 (*t*, $J = 12.0$, 2 H); 2.67–2.60 (*m*, 2 H); 2.43 (*s*, 3 H); 2.40–2.29 (*m*, 1 H); 1.86 (*q*, $J = 18.8$, 1 H). ^{13}C-NMR: 159.1; 144.2; 134.6; 132.0; 129.6; 129.2; 129.1; 127.8; 118.2; 113.8; 113.7; 72.5; 65.3; 63.5; 55.1; 39.1; 34.0; 21.5. HR-MS: 413.1393 ($[M + Na]^+$, $C_{12}H_{26}O_5S^+$; calc. 413.1399).

1-({[(3R)-3-Azidohex-5-en-1-yl]oxy}methyl)-4-methoxybenzene (**13**). To a soln. of 1**2** (2 g, 5.12 mmol) in dry DMF (20 ml) were added 5 equiv. of NaN_3 (1.6 g) portionwise at 70°, and this mixture was stirred for 6 h. After consumption of starting material (monitored by TLC), the mixture was diluted with H_2O and then extracted with AcOEt (3×30 ml). The org. layer was further washed with aq. sat. $NaHCO_3$ and aq. sat. NaCl, and dried (Na_2SO_4). The solvent was removed under vacuum. The crude product was purified by FC (SiO_2; hexane/AcOEt 9:1) to give **13** (79%). Pale-yellow liquid. $[\alpha]_D^{25} = -38$ ($c = 1.0$, $CHCl_3$). IR (KBr): 2923, 2855, 2100, 1513, 1248, 772. ^{1}H-NMR: 7.20 (*d*, $J = 8.3$, 2 H); 6.82 (*d*, $J = 9.0$, 2 H); 5.88–5.72 (*m*, 1 H); 5.17–5.07 (*m*, 2 H); 4.41 (*s*, 2 H); 3.80 (*s*, 3 H); 3.65–3.46 (*m*, 3 H); 2.32–2.25 (*m*, 2 H); 1.88–1.76 (*m*, 1 H); 1.68–1.56 (*m*, 1 H). ^{13}C-NMR: 159.5; 133.7; 130.2; 129.2; 118.3; 113.7; 72.9; 66.3; 59.1; 55.3; 55.1; 39.3; 34.1. HR-MS: 284.1369 ($[M + Na]^+$, $C_{14}H_{19}N_3O_2^+$; calc. 284.1371).

(3R)-3-Azidohex-5-en-1-ol (**8**). To a soln. of **13** (1 g, 3.83 mmol) in CH_2Cl_2/H_2O 9:1 (10 ml) was added DDQ (0.952 g, 4.21 mmol) at 0°. After stirring for 1 h, the mixture was filtered off, and the filtrate was washed with 5% $NaHCO_3$ soln. and brine, and dried (Na_2SO_4). The combined org. layers were evaporated to dryness to afford crude product, which was purified by FC to give **8** (80%). $[\alpha]_D^{25} = -113$ ($c = 1.0$, $CHCl_3$). IR (KBr): 3457, 2923, 2853, 2098, 1462. ^{1}H-NMR: 5.89–5.72 (*m*, 1 H); 5.22–5.14 (*m*, 2 H); 3.78 (*t*, $J = 10.9$, 2 H); 3.64–3.53 (*m*, 1 H); 2.47 (*m*, 2 H); 1.84–172 (*m*, 1 H); 1.70–1.52 (*m*, 1 H). ^{13}C-NMR: 133.6; 118.9; 59.8; 59.1; 39.1; 36.2. EI-MS: 141 (M^+).

(4R)-4-Azidohept-6-en-2-ol (**14**). *i*) To a soln. of **8** (0.500 g, 3.546 mmol) in 15 ml of CH_2Cl_2 at 0° were added $NaHCO_3$ (1.489 g, 17.73 mmol) and *Dess–Martin* periodinane (3 g, 7.09 mmol). The mixture was stirred at 0° for 2 h, and then *ca.* 10 ml of a 5:1 aq. sat. $NaHCO_3$ and aq. sat. $Na_2S_2O_3$ soln. were added. The mixture was diluted with Et_2O and stirred at r.t. until separation of the layers (45 min). The mixture was extracted with Et_2O (2×20 ml), and the combined org. layers were washed with cold 1M $NaHSO_4$ and dried (anh. Na_2SO_4). The solvent was removed under vacuum to obtain the crude aldehyde which was used for the next step without purification.

ii) In a 100-ml two-neck round-bottom flask 0.34 g (14.1 mmol), activated Mg was taken in dry Et_2O (5 ml), and MeI (0.8 ml, 14.18 mmol) was added, and the mixture was stirred for 30 min at r.t. After keeping this mixture at 0°, and the above crude aldehyde was added, the reaction was monitored by TLC. The reaction was quenched with aq. sat. NH_4Cl (3 ml), and the mixture was diluted with H_2O and extracted with AcOEt (2 × 20 ml). The solvent was removed under vacuum. The crude product was purified by FC (SiO_2; hexane/AcOEt 8:2) to give **6** (85%). Yellow liquid. $[\alpha]_D^{25} = -86$ ($c = 1.0$, $CHCl_3$). IR (KBr): 3381, 2923, 2854, 2106, 1460, 1254. ^{1}H-NMR: 5.88–5.74 (*m*, 1 H); 5.15 (*m*, 2 H), 4.03 (*m*, 1 H); 3.72–3.47 (*m*, 1 H); 2.41–2.27 (*m*, 2 H); 1.65–1.41 (*m*, 2 H); 1.23 (*d*, $J = 6.0$, 3 H). ^{13}C-NMR: 133.8; 118.9; 64.5; 59.2; 42.9; 38.6; 24.2. EI-MS: 155 (M^+).

*Benzyl [(4*R*)-6-Hydroxyhept-1-en-4-yl]carbamate* (**15**). Into a oven-dried 100-ml two-neck round-bottom flask, 2 equiv. of $LiAlH_4$ (0.092 g) were placed. To this ash-colored solid in dry THF (5 ml) was added a soln. of **14** (0.3 g, 1.9 mmol in dry THF (5 ml) over a period of 5 min at 0°. After stirring for 1 h, and reaction was quenched with aq. sat. $NaHCO_3$ (5 ml) soln. at 0°, 2 equiv. of Cbz-Cl (0.55 ml, 3.8 mmol) were added, and the mixture was stirred for 1 h. Then, the mixture was diluted with H_2O and extracted with AcOEt. The org. layer was washed with brine soln., dried (Na_2SO_4), and concentrated to obtain the crude product, which was purified by FC (SiO_2; hexane/AcOEt 7:3) to give **15** (0.330 g; 90%). Yellow liquid. $[\alpha]_D^{25} = -30$ ($c = 1.0$, $CHCl_3$). IR (KBr): 3325, 2965, 2925, 1694, 1534, 1262, 1074, 697. ^{1}H-NMR: 7.36–7.25 (*m*, 5 H); 5.84–5.66 (*m*, 1 H); 5.10 (*m*, 4 H); 3.98–3.65 (*m*, 2 H); 2.28–2.14 (*m*, 2 H); 1.50 (*m*, 1 H); 1.32 (*m*, 1 H); 1.13 (*d*, $J = 6.0$, 3 H). ^{13}C-NMR: 157.2; 136.4; 134.1; 128.5; 128.1; 118.2; 66.9; 63.4; 47.7; 45.1; 39.6; 22.9. HR- MS: 286.1413 ($[M + Na]^+$, $C_{15}H_{21}NO_3^+$; calc. 286.1411).

*Benzyl [(4*R*)-6-Oxohept-1-en-4-yl]carbamate* (**6**). To a soln. of **15** (0.200 g, 0.760 mmol) in 10 ml of CH_2Cl_2 were added $NaHCO_3$ (0.319 g, 3.802 mmol) and *Dess–Martin* periodinane (0.644, 1.520 mmol) at 0°. The mixture was stirred at 0° for 1 h, and then *ca.* 5 ml of a 5:1 mixture of aq. sat. $NaHCO_3$ and aq. sat. $Na_2S_2O_3$ soln. were added. The mixture was diluted with Et_2O and stirred at r.t. until separation of the layers (30 min). The mixture was extracted three times with Et_2O, and the combined org. layers were washed with cold 1M $NaHSO_4$ and dried (anh. Na_2SO_4). The solvent was removed under vacuum. The crude product was purified by FC (SiO_2; hexane/AcOEt 8:2) to give **6** (90%). White solid. M.p. 66–68°. $[\alpha]_D^{25} = -25.8$ ($c = 1.0$, $CHCl_3$). IR (KBr): 2922, 2953, 1699, 1532, 1259, 738. ^{1}H-NMR: 7.35–7.21 (*m*, 5 H); 5.79–5.62 (*m*, 1 H); 5.21–4.99 (*m*, 4 H); 3.95 (*m*, 1 H); 2.78–2.53 (*m*, 2 H); 2.39–2.26 (*m*, 2 H); 2.12 (*s*, 3 H). ^{13}C-NMR: 206.7; 155.6; 136.6; 134.2; 128.5; 128.0; 118.3; 66.6; 47.5; 46.4; 38.6; 30.4. HR-MS: 262.1148 ($[M + H]^+$, $C_{15}H_{19}NO_3^+$; calc. 262.1438).

*Benzyl [(4*R*,6*E*)-2,8-Dioxonon-6-en-4-yl]carbamate* (**5**). In a two-neck flask equipped with N_2 inlet, a magnetic stirring bar, and a rubber septum, was placed *Grubbs*' second-generation catalyst (0.016 g, 5 mol-%). A soln. of **6** (0.1 g, 0.386 mmol) and methyl vinyl ketone (0.081 g, 1.158 mmol) in CH_2Cl_2 (2 ml) were introduced at 40°, and the resulting pink soln. was stirred for 1 h. When TLC analysis indicated complete consumption of **6**, the mixture was exposed to air and concentrated to give the crude product, which was purified by FC (SiO_2; hexane/AcOEt 6:4) to give **5** (90%). Brown solid. M.p. 73–75°. $[\alpha]_D^{25} = -8.5$ ($c = 1.0$, $CHCl_3$). IR (KBr): 2925, 2854, 1711, 1533, 1257, 741. ^{1}H-NMR: 7.34–7.21 (*m*, 5 H); 6.74–6.58 (*m*, 1 H); 6.03 (*d*, $J = 16.6$, 1 H); 5.03 (*s*, 2 H); 4.13–3.93 (*m*, 1 H); 2.77–2.34 (*m*, 4 H); 2.14 (*s*, 3 H); 2.10 (*s*, 3 H). ^{13}C-NMR: 206.6; 197.7; 155.7; 142.9; 136.3; 133.5; 128.4; 128.0; 127.9; 66.6; 47.7; 46.8; 37.5; 30.4; 26.8. HR-MS: 326.1124 ($[M + Na]^+$, $C_{17}H_{21}NO_4^+$; calc. 326.1363).

*1-[(2*R*,6*R*)-6-Methylpiperidin-2-yl]propan-2-one* (*=(−)-Pinidinone*; **1**). To a stirred soln. of **5** (0.050 g) in AcOEt (5 ml) was added 10% Pd/C, and hydrogenation was performed under 1 atm pressure of H_2 at r.t. for 12 h. The mixture was filtered through *Celite*, and the filtrate was concentrated to obtain the crude product, which was purified by FC (SiO_2; CH_2Cl_2/MeOH 8:2) to give **1** (72%). Yellow oil. $[\alpha]_D^{25} = -3.6$ ($c = 0.5$, MeOH). IR (KBr): 3397, 2925, 2853, 1744, 1459, 1383, 1219. ^{1}H-NMR: 3.94–3.83 (*m*, 1 H); 3.45–3.38 (*m*, 1 H); 2.79 (*d*, $J = 6.0$, 2 H); 2.09 (*s*, 3 H); 1.72–1.45 (*m*, 4 H); 1.36–1.28 (*m*, 2 H); 1.11 (*d*, $J = 2.0$, 3 H). ^{13}C-NMR: 206.8; 55.1; 54.6; 54.3; 31.5; 30.1; 29.2; 23.5; 19.8. EI-MS: 155 (M^+).

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Received July 2, 2012