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REMOTE ACYCLIC STEREOCONTROL

CHIRAL SYNTHESIS OF (+)-PEDAMIDE

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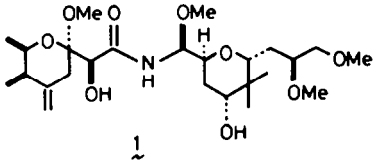
Abstract—Synthesis of optically active pedamide (**3**), one of the tetrahydropyran moieties of the potent insect poison pederine (**1**), has been accomplished through a new, remote controlled asymmetric reduction of a ketone as key step.

(+)-Pederine (**1**), a potent insect poison isolated from *Paedrus fuscipes*, exhibits remarkable physiological activities, such as inhibition of mitosis in HeLa cells and blocking of protein synthesis in 80S ribosomes at concentrations of 1–10 ng/ml.[1] The principle responsible for this action was first isolated independently by Ueta[2] and Pavan.[3] Detailed NMR spectral analysis[4] of the toxin, coupled with chemical evidence,[5] suggested that the structure was represented by **1** and this was confirmed by an X-ray crystallographic study by us.[6] The X-ray analysis also established the absolute configuration of **1**. Since the natural product is not readily available, a practical chemical synthesis of **1** seemed to be an attractive problem, because of its unconventional chemical structure and physiological properties. Recently we reported in a short form,[7] the first stereocontrolled total synthesis of **1**. This synthesis involved stereocontrolled construction of the two tetrahydropyran moieties, (+)-selenoacid **2** and (+)-benzoylpedamide (**3**), connection of them through an N-(1-methoxyalkyl) amide linkage, and elaboration of the target product. In this paper we wish to report the details of the effective chiral synthesis of one of the starting material pedamide (**3**) through a new, remote controlled acyclic asymmetric reduction (1, 5-induction) of a ketone.



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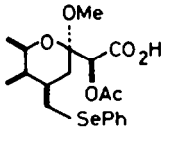

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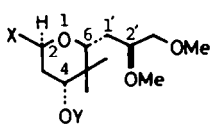
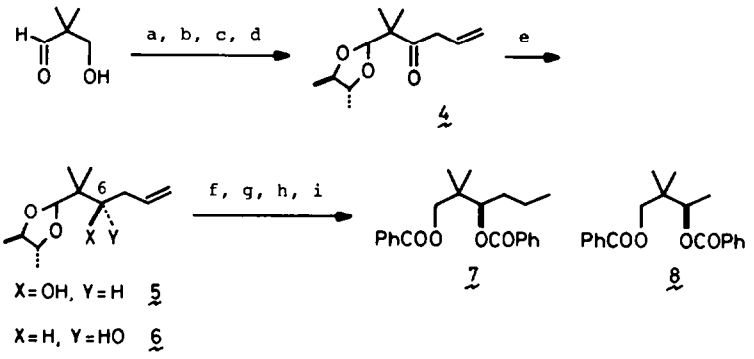


X=CONH$_2$, Y=COPh **3**

X=COH, Y=H **3a**

Formerly we reported also a stereocontrolled synthesis of racemic pedaldehyde (**3a**).[7b] However, adoption of this route to the synthesis of optically active pedaldehyde derivatives, such as **3**, was not suitable, since the sequence involved a compound with a plane of symmetry as a key intermediate. Therefore, new synthetic routes were investigated.

It turned out eventually that in the reduction of an optically active ketone **4**, which was prepared from 3-hydroxy-2, 2-dimethyl-propanal and (−)-(2*R*, 3*R*)-2, 3-butanediol (Scheme 1), a 1, 5-asymmetric induction took place with hydride reagents to give a (+)-alcohol **5**, having the desired 6*R*-configuration (CA numbering for pedamide). For the purpose of improving the optical yield, employing a variety of hydride reagents, the extent of the new asymmetric induction in the reduction of **4** were examined. The results are summarized in Table 1. The *R*-configuration of **5** was determined by leading it to a dibenzoate **7** and comparing its optical rotation with that of a closely related dibenzoate **8**.[8] The enantiometric excess was obtained by ^{1}H NMR spectra. By addition of Eu(fod)$_3$, unresolved signals (60 MHz) due to the acetal proton of each diastereoisomer were observed as separate singlet peaks. As can be seen in Table 1, complex hydrides which had Li^+ as counter ion in aprotic solvents gave in general relatively good selectivity. Further, use of more sterically hindered reagents resulted in less selective reduction. In cases of sterically hindered and less active reagents such as LiAlH(OtBu)$_3$ or LiAlH(OMe)$_3$ no reaction occurred at −78°. Among the reagents employed, $LiAlH_4$ turned out to give the best result to give **5** in 50% e.e. These results suggested a fairly congested transition state involving coordinated Li^+, such as **9** (Scheme 2). Since it was found that replacement of the allyl side chain of **4** by a propyl side chain had little influence on the degree of asymmetric induction and moreover, in the case of propyl side chain enantiometric excess was readily obtained by ^{1}H NMR, further investigations of this reduction were carried out using saturated ketone **10**. Temperature dependence and solvent effects of this reaction were examined employing $LiAlH_4$ as hydride reagent and results are summarized in Table 2. In all cases, main epimer obtained was alcohol **11**, which had *R*-configuration at the new chiral center. The *R*-configuration of **11** was ascertained by conversion of **5** into **11** as shown in Scheme 1. The degree of asymmetric induction raised by lowering the reaction temperature as expected. At −123° in ether, the



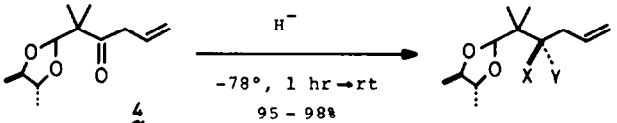
X=OH, Y=H **5**

X=H, Y=HO **6**

a: (-)-(2R,3R)-2,3-butanediol, p-TsOH·H_2O, PhH, reflux, 8 hr, b: PCC, AcONa, CH_2Cl_2, rt, 12 hr, c: CH_2=$CHCH_2MgBr$, ether, rt, 12 hr, d: Jones reagent, An, 0°, 30 min, e: $LiAlH_4$, ether, -78°, 2 hr, f: H_2, Pd-C, EtOH, 1 hr, g: 3N HCl, An, reflux, 5 hr, h: $LiAlH_4$, ether, rt, 1 hr, i: PhCOCl, Py, rt, 12 hr.

Scheme 1.

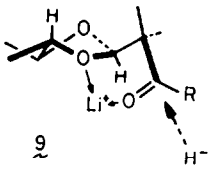
Table 1.



X=OH, Y=H **5**

X=H, Y=OH **6**

Conditions	5 : 6
$LiAlH_4$, ether	75 : 25
$LiAlH(OMe)_3$, ether	72 : 28
$LiAlH(OtBu)_3$, ether	63 : 37
$LiBH(iBu)_3$, THF	63 : 37
$NaBH_4$, EtOH	50 : 50
$AlH(iBu)_3$, PhMe	48 : 52



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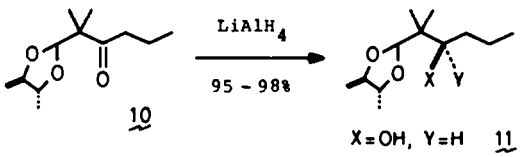
Scheme 2.

asymmetric induction took place in 70% e.e. Moreover, selectivity of the reduction was increased by employing an ether–PhMe solvent system. At −78°, the highest degree of the asymmetric induction was obtained in the ether–PhMe 1:1 mixture, giving **11** in 60% e.e. In contrast, more polar and solvating solvents than ether such as THF or Me_2O lowered the selectivity. These solvent effects and before mentioned superiority of lithium complex hydride reagents suggested that interaction between Li^+ and substrate plays an important role in this 1, 5-asymmetric induction. In fact the reaction in the presence of added 1 equiv LiBr increased the optical yield ($LiAlH_4$, ether, −100°, 2 hr, 66% e.e.). Ultimately the e.e. value as high as 98.5% was obtained by the use of (+)-(2*R*, 3*R*)-1, 4-dimethoxy-2,3-butanediol[9] as chiral source. Reduction of dimethoxydioxolane **13** ($LiAlH_4$, 1 equiv LiBr, ether–PhMe 1:1, −123°) afforded **14** in 98.5% e.e. and 97% yield. A plausible transition state for this case in depicted by **15** (Scheme 3). However, for practical reasons, synthesis of pedamide (**3**) was carried out employing (2*R*, 3*R*)-2,3-butanediol as chiral source. Under the most practically favorable conditions ($LiAlH_4$, ether–PhMe 1:1, −123°) the allylic compound **4** afforded **5** in 74% e.e. and 98% yield (Scheme 4).

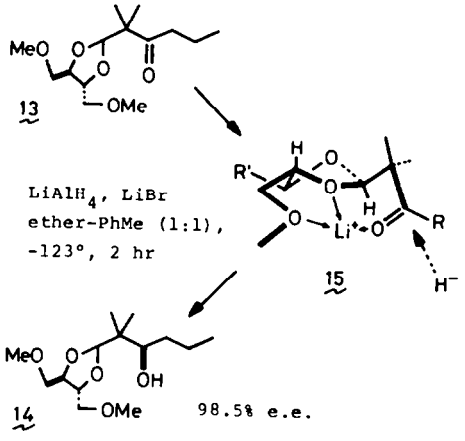
Although these two epimers were able to be separated by chromatography, the epimeric mixture (74% e.e.) was employed for subsequent steps for convenience. Sharpless epoxidation[7b,10] [$VO(AA)_2$, $tBuO_2H$] of **5** gave unsatisfactory result [(6*R**, 2′*S**):(6*R**, 2′*R**) < 3:1]. Therefore, **5** was converted into a methoxyketone **16**, in 76% overall yield by the sequence (1) protection of the C-6 hydroxyl group as benzyl ether, (2) nonstereoselective oxidation of the double bond employing mCPBA, (3) opening of the epoxide group using MeONa, and (4)

Table 2.



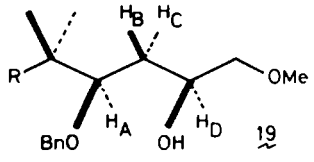
Conditions	11 : 12
ether, 25°, 2 hr	50 : 50
ether, -78°, 2 hr	75 : 25
ether, -100°, 2 hr	80 : 20
ether, -123°, 2 hr	85 : 15
ether-PhMe (75:25), -78°, 2 hr	78 : 22
ether-PhMe (50:50), -78°, 2 hr	80 : 20
ether-PhMe (25:75), -78°, 2 hr	54 : 46
PhMe, -40°, 4 hr[a]	50 : 50
THF, -78°, 2 hr	64 : 36
Me_2O, -78°, 2 hr	63 : 37

[a] 30% reaction.

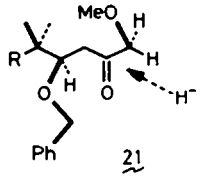


Scheme 3.

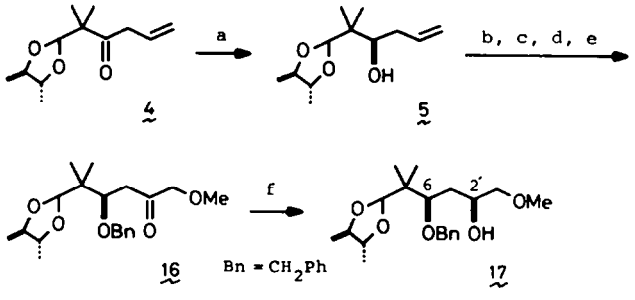
Collins oxidation (Scheme 4). We next examined a model hydride reduction of racemic methoxyketone **18**, which was prepared through a similar route to the optically active **16**, since the selectivity of this reaction was readily obtained by ^1H NMR. Peaks due to the methylene protons of the benzyl group of the products **19** and **20** were observed as ABq and A_2



respectively, at 60 MHz. The compound exhibiting the ABq was assumed[11] to have structure **19** at this stage, and this assumption was verified by leading **19** to racemic methyl pedate (**25**) through a similar route to the optically active **25**. The results of hydride reduction of **18** are summarized in Table 3. In all cases the desired *syn*-alcohol **19** was obtained as main epimer. In contrast to the before mentioned 1, 5-asymmetric induction, more sterically hindered reagent resulted in more selective induction. Furthermore similar selectivity as $LiAlH_4$ was obtained by employing $NaBH_4$ in ethanol. The selectivity of this reduction could be explained by assuming the stable conformation to be **21**. Since a methylene group is more bulky than a carbonyl O atom and **18** contains a quaternary C atom, **21** is a plausible main conformation of **18**. Nucleophilic attack of the hydride may occur from the less hindered side as shown in Scheme 5, even in the absence of the coordination effect, such as in the case of $NaBH_4$. Among the reduction conditions so far examined, $LiAlH(OtBu)_3$



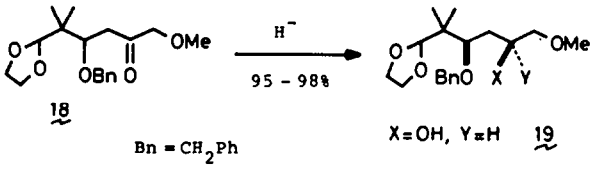
Scheme 5.



a: $LiAlH_4$, ether-PhMe (1:1), -123°, 2 hr, b: $PhCH_2Cl$, tAmONa, DMSO, rt, 2 hr, c: mCPBA, CH_2Cl_2, rt, 12 hr, d: MeONa, MeOH, rt, 2 days, e: Collins reagent, CH_2Cl_2, rt, 2 hr, f: $LiAlH(OtBu)_3$, ether, -78°, 1 hr.

Scheme 4.

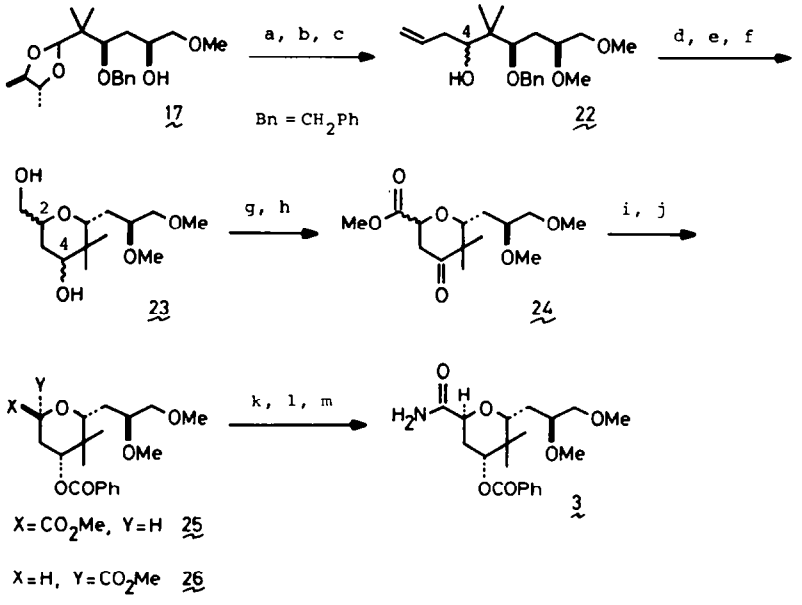
Table 3.



Conditions	19 : 20
$LiAlH_4$, ether, -78°, 1 hr	83 : 17
$LiAlH_4$, ether, -123°, 1 hr	85 : 14
$Zn(BH_4)_2$, ether, -78°, 1 hr→rt	87 : 13
$NaBH_4$, EtOH, -78°, 1 hr	80 : 20
$LiAlH(OtBu)_3$, ether, -78°, 1 hr	92 : 8

in ether at −78° gave the highest stereoselectivity, the ratio of **19** to **20** being 92 to 8. Under these conditions, 1, 3-asymmetric induction of **16** was successfully performed to afford in 95% yield an (−)-alcohol **17** (Scheme 4), which possessed the desired S-configuration [(6*R**, 2′*S**):(6*R**, 2′*R**) > 10:1] at the new chiral center (C-2′).

Alcohol **17** thus obtained was converted into tetrahydropyran derivative **23** in 46% overall yield by the sequence (1) methylation of the new OH group, (2) removal of the acetal group, (3) Grignard reaction, (4) removal of the benzyl group by Na in liquid NH_3, (5) oxidation of the olefin employing mCPBA, and (6) successive acid treatment (Scheme 6). Although the stereochemistry at C-2 and C-4 (newly formed chiral centers of **23**) were not homogeneous, this was not a serious problem, because stereocontrol at these centers on the 6-membered ring was readily performed as mentioned below. For the purpose of correcting the stereochemistry at C-4, **23** was converted into ketoester **24** in 75% yield through Jones oxidation, followed by esterification. Reduction of **24** with $NaBH_4$ afforded predominantly the desired α-alcohol and after protection of the OH group as



a: MeI, NaH, PhH, reflux, 2 hr, b: 3N HCl, An, reflux, 5 hr, c: CH_2=$CHCH_2MgBr$, ether, rt, 12 hr, d: Na, liquid NH_3, -78°, 20 min, e: mCPBA, CH_2Cl_2, rt, 12 hr, f: p-TsOH·H_2O, PhH, reflux, 12 hr, g: Jones reagent, An, rt, 12 hr, h: CH_2N_2, ether, rt, i: $NaBH_4$, EtOH, -78°, 30 min, j: PhCOCl, Py, rt, 12 hr, k: Et_3N, H_2O, MeOH, rt, 12 hr, l: $SOCl_2$, DMF, CH_2Cl_2, reflux, 3 hr, m: NH_3, CH_2Cl_2, 0°, 30 min.

Scheme 6.

benzoate, a 1:1 mixture of methyl pedate (**25**) and methyl 2-epipedate (**26**) was obtained in 85% overall yield (Scheme 6). These epimers were able to be separated by silica gel chromatography. Conversion of **26** into **25** was effected by enolization and subsequent kinetically controlled protonation to give a 54% yield of **25** and a 12% yield of **26**. After seeding a few crystals of racemic **25** and removal of separated racemic crystals (83%), optically enriched (+)-**25** was transformed to (+)-benzoylpedamide (**3**) in 79% overall yield by the following sequence; (1) hydrolysis of the methoxy-CO group, (2) acid chloride formation, and (3) amidation (Scheme 6). Optically pure (+)-**3** was obtained by recrystallization from hexane (79%). Optical purity was confirmed by ^{1}H NMR spectra of **3** in the presence of chiral shift reagent, Eu(tfc)$_3$.

EXPERIMENTAL

IR spectra were recorded on a JASCO model IR-S spectrophotometer and NMR spectra were measured at 60 MHz (Hitachi R-20B). Chemical shifts are reported in ppm (δ) relative to TMS as internal standard. Optical rotations were determined on a JASCO model DIP-SL polarimeter.

(4R, 5R)-4, 5-*Dimethyl*-2-(1, 1-*dimethyl*-2-*hydroxy*-4-*pentenyl*)-1, 3-*dioxolane*

A 1:1 *mixture of* **5** *and* **6**. To a stirred mixture of isobutylaldehyde (28 g, 0.39 mol) and 37% formalin (42 g, 0.52 mol) were added K_2CO_3 (22 g, 0.16 mol) by portions under cooling in an ice bath, keeping the soln at room temp. Stirring was continued at room temp for additional 30 min. The mixture separated in two phases on being kept standed. The organic layer was removed and the aqueous layer was extracted with PhH. The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo* to give 32 g (81%) of 3-hydroxy-2,2-dimethylpropanal.

3-Hydroxy-2,2-dimethylpropanal (32 g, 0.31 mol) was dissolved in PhH (140 ml) containing (−)-(2*R*, 3*R*)-2,3-butanediol (26 g, 0.29 mol) and *p*-TsOH·H$_2$O (0.70 g, 3.7 mmol) at room temp. The mixture was heated at reflux under a Dean–Stark apparatus for 8 hr. After cooling, the mixture was washed successively with 2N NaOH and brine, dried over Na_2SO_4, and evaporated *in vacuo*.

To a soln of the residual oil in CH_2Cl_2 (400 ml) were added PCC (240 g, 1.1 mol) and AcONa (3.7 g, 45 mmol) successively at room temp. The mixture was stirred at room temp for 12 hr. To the mixture was added ether (400 ml) and the ethereal soln was removed by decantation. The ppt was collected and extracted with ether. The combined ethereal soln was washed successively with 2N NaOH and brine, and dried over Na_2SO_4, and the solv was distilled off at atmospheric pressure. Distillation of the residual oil under reduced pressure gave 32 g (64%) of (4*R*, 5*R*)-4,5-dimethyl-2-(1,1-dimethyl-2-oxoethyl)-1,3-dioxolane.

To a stirred soln of the above dioxolane (32 g, 0.19 mol) in ether (140 ml) cooled to 0° was added by portions a soln of allyl magnesium bromide [prepared from Mg (24 g, 1.0 mol) and allyl bromide (121 g, 1.0 mmol) in ether (1000 ml)]. After stirring was continued for 12 hr at room temp, the reaction mixture was poured into ice–water and sat NH_4Cl aq was added to the mixture until all the solid materials dissolved. The ethereal layer was separated and the aqueous layer was extracted with ether. The combined ethereal phases were washed with brine and dried over Na_2SO_4. Removal of the solv *in vacuo* gave a crude product. Chromatography of the crude product on silica gel (PhH–AcOEt, 90:10) gave 31 g (78%) of a 1:1 mixture of **5** and **6**: IR (neat) 3400, 2950, 1105, 1000, 920 cm^{-1}; ^{1}H NMR (CCl_4) δ 0.83, 0.88 (each 3H, s), 1.17, 1.26 (each 3H, d, 7 Hz), 2.70 (1H, bs), 4.75 (1H, s). (Found C, 66.95; H, 10.31%. Calc for $C_{12}H_{22}O_3$: C, 67.25; H, 10.35%.)

Alcohol **5** (50% e.e.)

A soln of the 1:1 mixture of **5** and **6** (10 g, 47 mmol) in acetone (200 ml) was cooled to 0° and Jones reagent was added dropwise until the faint red color persisted. After stirring at 0° and for 30 min, the excess Jones reagent was destroyed by the addition of i-PrOH. The ppt was filtered off and washed with ether. The combined filtrates were concentrated *in vacuo* and the residue was extracted with ether. The combined extracts were dried over Na_2SO_4 and removal of the solv *in vacuo* gave 9.6 g (97%) of **4**.

To a suspension of $LiAlH_4$ (18 mg, 0.47 mmol) in ether (2.0 ml) cooled to −78° was added a soln of **4** (50 mg, 0.24 mmol) in ether (0.5 ml) cooled to −78°. After stirring was continued at −78° for 1 hr and the temp allowed to rise to room temp, the excess hydride was destroyed by the addition of water (1 ml). The mixture was neutralized with 1N HCl and extracted with ether and the extracts were dried over Na_2SO_4. Removal of the solv *in vacuo* gave 49 mg (97%) of **5** in 50% e.e. by NMR in the presence of Eu(fod)$_3$; see text.

(4R, 5R)-4, 5-*Dimethyl*-2-(1, 1-*dimethyl*-2-*hydroxypentyl*)-1,3-*dioxolane*

A 1:1 *mixture of* **11** *and* **12**. To a suspension of 10% Pd–C (0.2 g) in AcOEt (200 ml) was added a soln of the 1:1 mixture of **5** and **6** (10 g, 47 mmol) in AcOEt (50 ml) under H_2 atmosphere at room temp. After stirring was continued at room temp for 1 hr, the mixture was filtered and evaporated *in vacuo* to give 10 g (99%) of a 1:1 mixture of **11** and **12**; IR (neat) 3500, 1100 cm^{-1}; ^{1}H NMR (CCl_4) δ 0.80, 0.83 (each 3H, s), 0.90 (3H, t, 7 Hz), 1.19, 1.26 (each 3H, d, 7 Hz), 2.20 (1H, bs), 4.70 (1H, s). (Found: C, 66.41; H, 11.27%. Calc for $C_{12}H_{24}O_3$: C, 66.63; H, 11.18%.)

Alcohol **11** (70% e.e.)

A soln of the 1:1 mixture of **11** and **12** (10 g, 46 mmol) in acetone (200 ml) was cooled to 0° and treated dropwise with Jones reagent until the faint red color persisted. After stirring at 0° for 30 min, the excess Jones reagent was destroyed by the addition of i-PrOH. Working up as above gave 9.5 g (96%) of **10**.

To a suspension of $LiAlH_4$ (18 mg, 0.47 mmol) in ether (2.0 ml) cooled to −123° was added a soln of **10** (50 mg, 0.23 mmol) in ether (0.5 ml) semi-solidified by liquid N_2. After stirring was continued at −123° for 2 hr, the excess hydride was destroyed by the addition of water (1 ml). The mixture was worked up as before to give 49 mg (97%) of **11** in 70% e.e.

Alcohol **11** (60% e.e.)

To a suspension of $LiAlH_4$ (18 mg, 0.47 mmol) in ether–PhMe (1:1, 2.0 ml) cooled at −78° was added a soln of **10** (50 mg, 0.23 mmol) in ether–PhMe (1:1, 0.5 ml) cooled to −78°. After stirring was continued at −78° for 2 hr, the reaction mixture was treated as before to give 48 mg (95%) of **11** in 60% e.e.

Alcohol **11** (66% e.e.)

To a suspension of LiBr (20 mg, 0.23 mmol) in ether (0.5 ml) cooled to −100° was added a soln of **10** (50 mg, 0.23 mmol) in ether (1.0 ml). After stirring was continued at −100° for 1 hr, a suspension of $LiAlH_4$ (18 mg, 0.47 mmol) in ether (1.0 ml) cooled to −100° was added by a syringe. After stirring was continued at −100° for 2 hr, the mixture was processed as above to afford 48 mg (95%) of **11** in 66% e.e.

(4R, 5R)-4, 5-*Bis*(*methoxymethyl*)-2-(1, 1-*dimethyl*-2-*hydroxypentyl*)-1, 3-*dioxolane*

A 1:1 *mixture of* **14** *and its epimer*. A 1:1 mixture of **14** and its epimer was prepared from 3-hydroxy-2,2-dimethylpropanal by a procedure similar to (4*R*, 5*R*)-4,5-dimethyl-2-(1, 1-dimethyl-2-hydroxypentyl)-1, 3-dioxolane; a 1:1 mixture of **11** and **12**, employing (+)-(2*R*, 3*R*)-1,4-

dimethoxy-2,3-butanediol instead of (2*R*, 3*R*)-2, 3-butanediol. The mixture of **14** and its epimer: ^{1}H NMR (CCl_4) δ 0.81, 0.87 (each 3H, s), 0.91 (3H, t, 7 Hz), 2.47 (1H, bs), 3.32 (6H, s), 4.70 (1H, s). Benzyl ether of the mixture: IR (neat) 1190, 1100 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.87, 0.98 (each 3H, s), 0.95 (3H, t, 7 Hz), 3.30, 3.37 (total 3H, each s), 3.39 (3H, s), 4.59, 4.61 (total 2H, each s), 4.99, 5.04 (total 1H, each s). (Found: C, 68.91; H, 9.26%. Calc for $C_{21}H_{34}O_5$: C, 68.82; H, 9.35%.)

Alcohol **14** (98.5% e.e.)

A soln of the 1:1 mixture of **14** and its epimer (0.50 g, 1.8 mmol) in acetone (10 ml) was cooled to 0° and treated dropwise with Jones reagent until the faint red color persisted. After stirring at 0° for 30 min, the excess Jones reagent was destroyed by the addition of i-PrOH. Working up as usual gave 0.48 g (97%) of **13**.

To a suspension of LiBr (16 mg, 0.18 mmol) in ether–PhMe (1:1, 0.5 ml) cooled −123° was added a soln of **13** (50 mg, 0.18 mmol) in ether–PhMe (1:1, 1.0 ml). After stirring was continued at −123° for 1 hr, a suspension of $LiAlH_4$ (18 mg, 0.47 mmol) in ether–PhMe (1:1, 1.0 ml) cooled to −123° was added by a syringe. After stirring was continued at −123° for 2 hr, similar treatment as before afforded 49 mg (97%) of **14** in 98.5% e.e.

Alcohol **5** (74% e.e.)

To a suspension of $LiAlH_4$ (2.6 g, 69 mmol) in ether–PhMe (1:1, 325 ml) cooled to −123° was added a soln of **4** (6.5 g, 31 mmol) in ether–PhMe (1:1, 13 ml) semisolidified by liquid N_2. After stirring was continued at −123° for 2 hr, the excess hydride was destroyed by the addition of water (130 ml). Successive similar treatments as above gave 6.4 g (98%) of **5** in 74% e.e.; $[\alpha]_D^{24}$ +8.40° (1.10, $CHCl_3$).

(−)-*Alcohol* **17**

To a soln of **5** (9.7 g, 45 mmol, 74% e.e.) and *t*-AmONa (9.8 g, 89 mmol) in DMSO (100 ml) was added $PhCH_2Cl$ (6.6 g, 52 mmol) at room temp. After stirring was continued at room temp for 2 hr, water (300 ml) was added and the product was extracted with ether. The ethereal soln was washed with brine and dried over Na_2SO_4. Removal of the solv *in vacuo* gave a crude product. Chromatography of the crude product on silica gel (PhH–AcOEt, 97:3) gave 13.2 g (96%) of a benzyl ether.

To a soln of the benzyl ether (13.2 g, 43 mmol) in CH_2Cl_2 (90 ml) was added mCPBA (10.3 g, 52 mmol, 85%) at room temp. The mixture was stirred at room temp for 12 hr. To the mixture was added ether (630 ml) and the soln was washed successively with 2N NaOH and brine and dried over Na_2SO_4. Removal of the solv *in vacuo* gave 13.7 g (99%) of an epoxide.

To a soln of MeONa in MeOH [prepared from Na (3.1 g, 0.13 mol) and MeOH (90 ml)] was added a soln of the epoxide (13.7 g, 43 mmol) in PhH (90 ml) at room temp. Stirring was continued at room temp for 2 days. After evaporation of MeOH *in vacuo*, water (90 ml) was added and the product was extracted with ether. The ethereal soln was washed with brine and dried over Na_2SO_4. Removal of the solv *in vacuo* gave 14.3 g (95%) of a 1:1 mixture of **17** and its C-2′ epimer.

To a suspension of Collins reagent in CH_2Cl_2 [prepared from CrO_3 (24.6 g, 0.25 mol) and pyridine (39.4 g, 0.50 mol) in CH_2Cl_2 (600 ml) at room temp for 15 min] was added at once a soln of the 1:1 mixture of **17** and its C-2′ epimer (14.3 g, 41 mmol) in CH_2Cl_2 (20 ml) at room temp. The mixture was stirred at room temp for 2 hr. After organic layer was removed by decantation, the ppt was collected and extracted with ether. The combined organic layers were washed successively with 2N NaOH and brine and dried over Na_2SO_4. Removal of the solv *in vacuo* gave a crude product. Chromatography of the product on silica gel (PhH–AcOEt, 95:5) gave 12.0 g (84%) of a methoxy ketone **16**.

To a suspension of $LiAlH(OtBu)_3$ in ether [prepared from $LiAlH_4$ (3.0 g, 79 mmol) and t-BuOH (17.6 g, 0.24 mol) in ether (130 ml) at 0° for 30 min] cooled to −78° was added dropwise a soln of **16** (12.0 g, 34 mmol) in ether (30 ml) over 10 min. After stirring was continued at −78° for 1 hr, water (20 ml) and 1N HCl (20 ml) were added to the mixture. The ethereal layer was separated and the aqueous layer was extracted with ether. The combined ethereal phases were washed with brine and dried over Na_2SO_4. Removal of the solv *in vacuo* gave 11.5 g (95%) of alcohol **17**; $[\alpha]_D^{22}$ −16.6° (c 1.00, $CHCl_3$); IR (neat) 3400, 1100, 740, 690 cm^{-1}; ^{1}H NMR (CCl_4) δ 0.81, 0.95 (each 3H, s), 1.16, 1.25 (each 3H, d, 7 Hz), 2.70 (1H, bs), 4.41, 4.67 (each 1H, d, 11 Hz), 4.86 (1H, s), 7.17 (5H, s). (Found: C, 67.96; H, 9.31%. Calc for $C_{20}H_{32}O_5$: C, 68.15; H, 9.15%.)

Methyl pedate (**25**) *and methyl 2-epipedate* (**26**)

To a suspension of NaH (3.9 g, 0.10 mol, 60% paraffin oil dispersion washed with PhH) in PhH (350 ml) was added a soln of **17** (11.5 g, 33 mmol) in PhH (50 ml) at room temp. The mixture was heated at reflux for 10 min. After cooling, MeI (14.2 g, 0.10 mol) was added at room temp and the reaction mixture was heated at reflux for 2 hr, and the mixture was cooled and then poured by portions into ice-water. The product was extracted with PhH. The extracts were washed with brine, dried over Na_2SO_4, and evaporation *in vacuo* to give 11.1 g (93%) of a methyl ether.

To a soln of the methyl ether (11.1 g, 30 mmol) in acetone (1250 ml) was added 3N HCl (250 ml) at room temp. The mixture was heated at reflux for 5 hr. After cooling, acetone was removed off *in vacuo* and the product was extracted with ether. The ethereal soln was washed with brine and dried over Na_2SO_4. Removal of the solv *in vacuo* gave 8.2 g (92%) of an aldehyde.

To a stirred soln of the aldehyde (8.2 g, 28 mmol) in ether (350 ml) cooled to 0° was added by portions a soln of allylmagunesium bromide. After stirring was continued for 12 hr at room temp, the reaction mixture was worked up as before to give a crude product. Chromatography of the crude product on silica gel (PhH–AcOEt, 90:10) gave 8.0 g (85%) of a benzyloxyalcohol **22**.

Sodium metal (3.0 g, 0.13 mol) was dissolved in liquid NH_3 (260 ml) at −78°. To the resultant blue soln was added a soln of **22** (8.0 g, 24 mmol) in ether (30 ml) at −78°. After stirring was continued at −78° for 20 min, solid NH_4Cl was added in small portions until the blue color disappeared and then the NH_3 was left to evaporate. The residue was diluted with water and extracted with AcOEt. The extracts were washed with brine and dried over Na_2SO_4. Removal of the solv *in vacuo* gave 4.3 g (73%) of a diol.

To a soln of the diol (4.3 g, 17 mmol) in CH_2Cl_2 (40 ml) was added mCPBA (4.3 g, 21 mmol, 85%) at room temp. The mixture was stirred at room temp for 12 hr. To the mixture was added ether (280 ml) and the soln was washed successively with 2N NaOH and brine, dried over Na_2SO_4, and evaporated *in vacuo*.

To a soln of the residual oil in PhH (150 ml) was added *p*-TsOH·H_2O (0.27 g, 1.4 mmol) at room temp and the mixture was heated at reflux for 12 hr. After evaporation of PhH in vacuo, chromatography of the residual oil on silica gel (AcOEt) gave 3.9 g (85%) of a tetrahydropyran derivative **23**.

A soln of **23** (3.9 g, 15 mmol) in acetone (80 ml) was cooled to 0° and treated with Jones reagent by portions until the faint red color persisted. After stirring at room temp for 12 hr, the excess Jones reagent was destroyed by the addition of *i*-PrOH. The ppt was filtered off and washed with AcOEt. The combined filtrates were concentrated *in vacuo* and the residue was extracted with AcOEt. The extracts were dried over Na_2SO_4. Removal of the solv *in vacuo* left crude acid, which was dissolved in ether (50 ml) and esterified with an ethereal soln of diazomethane. Evap-

oration of the solv *in vacuo* afforded crude ketoester, which was purified by chromatography on silica gel (AcOEt) to yield 3.2 g (75%) of a ketoester **24**.

To a soln of **24** (3.2 g, 11 mmol) in EtOH (200 ml) cooled to −78° was added $NaBH_4$ (1.0 g, 26 mmol). The sitrring was continued at −78° for 30 min and the reaction was quenched by the addition of AcOH. After evaporation of EtOH *in vacuo*, water was added and the product was extracted with AcOEt. The extracts were washed with brine and dried over Na_2SO_4. Removal of the solv *in vacuo* gave 2.9 g (90%) of an α-alcohol.

The α-alcohol (2.9 g, 10 mmol) was dissolved in pyridine (30 ml) and treated with PhCOCl (1.7 g, 12 mmol) at room temp for 12 hr. To the mixture was added MeOH (5 ml) and the solv was removed *in vacuo*. The residue was diluted with AcOEt and the soln was washed with 1N HCl and brine and dried over Na_2SO_4. After evaporation *in vacuo*, the crude product was chromatographed on silica gel (PhH–AcOEt, 80:20) to give 1.9 g (48%) of methyl pedate (**25**) and 1.8 g (46%) of **26**. **25**: IR (neat) 3020, 1740, 1720, 1605, 1590 cm^{-1}; ^1H NMR (CCl_4) δ 0.82, 1.07 (each 3H, s), 3.30 (6H, s), 3.77 (3H, s), 4.43 (1H, dd, 2 and 6 Hz), 4.78 (1H, dd, 5 and 12 Hz). (Found: C, 63.75; H, 7.56%). Calc for $C_{21}H_{30}O_7$: C, 63.94; H, 7.66%.) **26**: IR (neat) 3020, 1740, 1720, 1605, 1590 cm^{-1}; ^1H NMR (CCl_4) δ 0.92, 1.12, 3.29, 3.32, 3.68 (each 3H, s), 4.02 (1H, dd, 4 and 12 Hz), 4.90 (1H, dd, 5 and 12 Hz). (Found: C, 63.77; H, 7.66%. Calc for $C_{21}H_{30}O_7$: C, 63.94; H, 7.66%.)

Conversion of **26** *into* **25**

To a stirred soln of LDA [generated by the addition of n-BuLi (1.0ml, 1.6 mmol, 15% hexane soln) to a soln of $(i\text{-Pr})_2NH$ (0.21 g, 2.1 mmol) in THF (3.0 ml) at 0°] was added a soln of **26** (0.16 g, 0.41 mmol) in THF (1.5 ml) at −78°. Stirring was continued at −78° for 20 min and AcOH (0.5 ml) was added. After 10 min, the mixture was diluted with AcOEt. The soln was washed with brine, dried over Na_2SO_4, and evaporated *in vacuo*. Chromatography of the crude product on silica gel (PhH–AcOEt, 80:20) gave 86 mg (54%) of isomeric **25** and 19 mg (12%) of unchanged **26**.

(+)-*Benzoylpedamide* (**3**)

To a soln of **25** (1.0 g, 2.5 mmol) in hexane (20 ml) were added a few crystals of racemic **25**. After the suspension was set aside at 4° for 12 hr, separated racemic crystals were removed and the mother liquor was concentrated *in vacuo* to afford 0.83 g (83%) of optically purified **25**, which had $[\alpha]_D^{30}$ + 27.9° (*c* 2.60, $CHCl_3$).

To a soln of the optically enriched **25** (0.83 g, 2.1 mmol) in MeOH (18 ml) were added water (54 ml) and Et_3N (18 ml) at room temp. After stirring was continued at room temp for 12 hr, the solv was evaporated *in vacuo*.

To a soln of residual oil in CH_2Cl_2 (50 ml) were added $SOCl_2$ (8.2 g, 69 mmol) and DMF (1.0 ml) at room temp. The mixture was then heated at reflux for 3 hr. After cooling, the solv and excess $SOCl_2$ were evaporated *in vacuo*.

To the residual oil was added CH_2Cl_2 (50 ml) and the soln was cooled to 0°. Gas NH_3 was bubbled through the soln for 30 min at 0°. The soln was washed with brine, dried over Na_2SO_4, and evaporated *in vacuo*. Chromatography of the crude oil on silica gel (PhH–AcOEt, 50:50) gave 0.63 g (79%) of (+)-**3**, which was recrystallized from hexane to give 0.50 g (79%) of optically pure **3**: mp (uncorrected) 137–138°; $[\alpha]_D^{28}$ + 15.9° (*c* 3.24, $CHCl_3$); IR (nujol) 3420, 3340, 1725, 1685, 1610 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.94, 1.90, 3.36, 3.41 (each 3H, s), 4.46 (1H, dd, 3 and 6 Hz), 4.97 (1H, dd, 5 and 11 Hz). (Found: C, 63.12; H, 7.74; N, 3.67%. Calc for $C_{20}H_{29}O_6N$: C, 63.30; H, 7.70; N, 3.69%.)

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[11]The assumption is based on the ^1H NMR spectral data of **19** and **20**. The 400 MHz spectrum ($CDCl_3$) of **19** showed peaks due to H_A, H_B, H_C, and H_D at δ 3.69, 1.68, 1.79, and 3.96 respectively, with J_{BC} = 13.0 Hz, $J_{AB} = J_{BD}$ = 8.5 Hz, $J_{AC} = J_{CD}$ = 4.0 Hz. These data are compatible with stereostructure **19**. On the contrary the C-2′ epimer exhibited peaks at δ 1.59 (H_B) and 1.54 (H_C) with J_{BC} = 13.0 Hz, $J_{AB} = J_{CD}$ = 9.0 Hz, $J_{AC} = J_{BC}$ = 3.0 Hz.