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STEREOCHEMICAL STUDIES—LVII[1]

SYNTHESIS OF OPTICALLY ACTIVE COMPOUNDS BY THE NOVEL USE OF *MESO*-COMPOUNDS—1. EFFICIENT SYNTHESIS OF TWO STRUCTURAL TYPES OF OPTICALLY PURE PROSTAGLANDIN INTERMEDIATES.[2]

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Abstract—With an aim to overcome several inefficient aspects of ordinary methods of preparing optically active compounds, we have developed a new method which recommends utilization of symmetrically functionalized *meso*-compounds in place of racemic compounds.

As shown in Scheme 1, when the *meso-compound* (**I**) is monofunctionalized by an optically active functional group (**A**) and each of the formed diastereomers (**II** and **III**) is subjected to further chemical elaborations including protective group transposition, it is theoretically possible to convert the total amount of the starting material (**I**) into the requisite optically pure product (**VI** or **VII**) by selecting synthetic schemes.

By employing this novel concept, two structural types of the prostaglandin intermediates ((−)- and (+)-**2a,b**) have been prepared from the *meso*-diols (**1a, b**) by way of the two diastereomeric monoesters (**13a, b** and **14a, b**) which are produced by the reactions of **1a, b** with N-mesyl- and N-phthaloyl-(S)-phenylalanyl chloride (**3a, b**).

The preparation of an optically active compound is usually examined by employing one of the conventional three methods each with intrinsic disadvantages: (1) resolution of racemic compound; (2) chemical transformation from readily available optically active compound; (3) asymmetric synthesis.

Thus, when resolution of a racemic compound is attempted, the yield of desired enantiomer cannot theoretically exceed 50% even if a set of two diastereomers are separated, and the undesired enantiomer is completely useless unless this isomer involves one asymmetric centre which can easily racemize. Moreover, in the case where only one diastereomer can be obtained in a pure crystalline form, the possibility that the desired enantiomer can be derived from the crystalline diastereomer is just 50%, and when the derived enantiomer has the opposite absolute configuration to that desired, it is necessary to attempt the preparation of a diastereomeric mixture by employing a resolving agent which is antipodal to that utilized before. However, resolving agents which are available as a set of two enantiomers, are limited.

In the preparation of an optically active compound by chemical transformation from a readily available optically active compound, the total amount of the starting material can be transformed to the desired final product. However, varieties of readily available optically active compounds being usable as starting materials in large quantities, are limited to α-amino acids, sugars, and terpenes, and reactions which have been established to proceed without racemization should be selectively utilized for each synthetic step.

Asymmetric synthesis can produce theoretically optically pure compounds in 100% yield, and can reduce one synthetic step when compared with the resolution method. Many asymmetric syntheses employing catalytic or stoichiometric amounts of chiral sources have been reported.[3] However, considering chemical and optical yields, availability of chiral sources, and experimental procedures, the number of asymmetric syntheses which seemingly have practical values is quite small.

Taking these facts into account, an ideal method of preparing optically active compound should fullfil the following criteria:

(1) It should be theoretically possible to transform a total amount of the achiral starting material into the desired optically pure compound.

(2) Irrespective of the absolute configuration of the optically active agent indispensable for producing optically active compounds one enantiomeric agent being available, can always afford the desired optically pure compound.

As a method which might agree with above requirements, the authors have developed an entirely new method which utilizes a *meso*-compound having a symmetric structure.

This report outlines the new method and the preparation of two structural types of prostaglandin (PG) intermediates.[4]

RESULTS AND DISCUSSION

I. *Strategy of the novel method of preparing an optically active compound*

As shown in Scheme 1, monofunctionalization of the *meso*-compound (**I**) with the optically active functional group (**A**) gives a mixture of the two diastereomers (**II** and **III**). In a similar way to the resolution of a racemic compound, the diastereomeric mixture can be separated into each component (**II** and **III**) by fractional recrystallization or chromatography. The compound **IV** which can be readily derived from **II** by successive introduction of the functional group (**B**) chemically discriminated from **A** and removal of **A**, has a structure enantiomeric to starting **II** and having an absolute configuration equivalent to **III**. Therefore, when the desired optically pure compound (**VI**) can be obtained from **IV** by chemical elaborations, it is theoretically possible to prepare the compound **VII** enantiomeric to **VI**, from **II** by similar reactions. In a similar manner, the preparation of an enantiomeric pair of **VI** and **VII** can be accomplished from **III** directly and by way of **V**. Accordingly, if **II** and **III** are completely separated, it is theoretically possible to convert the total amount of **I** into the desired enantiomer (**VI** or **VII**) in 100% yield by selecting possible reaction schemes. Therefore, being different from the usual resolution of racemic compounds, an enantiomeric pair of resolving agents is not necessary and one enantiomer of optically active agent is enough for producing the desired optically pure product (**VI** or **VII**).

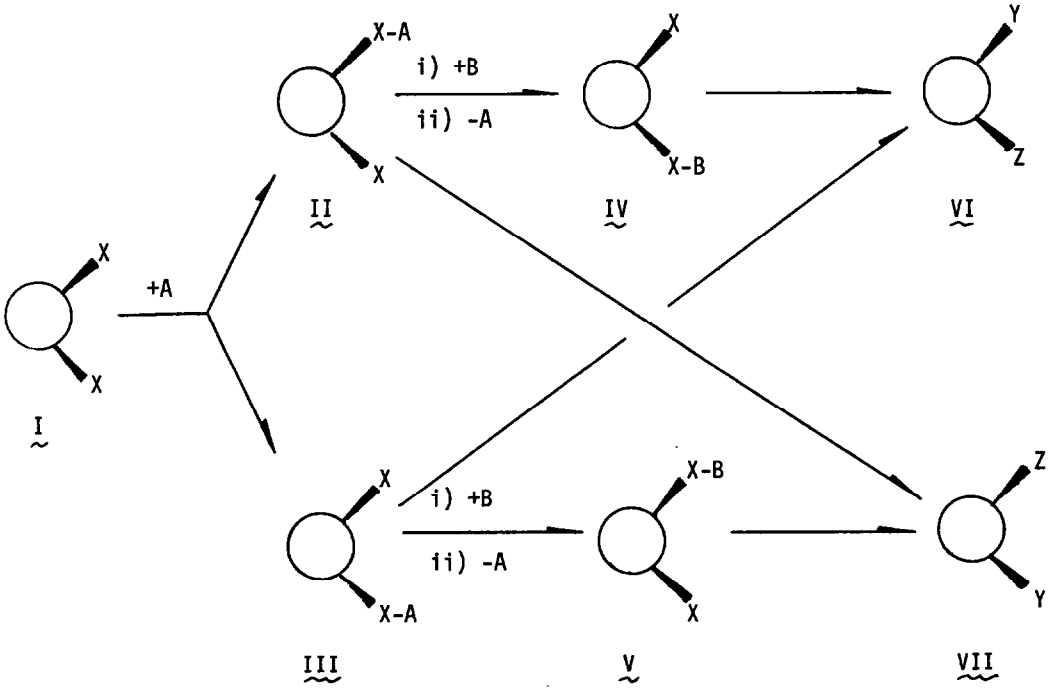
After we developed this strategy, Fischli, *et al.*[5] published a similar synthetic method. In their case, an enantiomeric pair of optically pure prostaglandin intermediates was synthesized by a long synthetic Scheme (13 steps) from one of the two diastereomers, obtainable from a *meso*-compound in a pure state. As our strategy aims to separate two diastereomers (**II** and **III**) and to utilize the total amount of the starting material (**I**) for the preparation of the desired optically pure enantiomer (**VI** or **VII**), it is more economical and effective than the method of Fischli *et al.*[5,6]

This report describes the realization of our method by separating **II** and **III** prepared using *cis*-2-cyclopentene-1,4-diol (**1a**)[7] and *cis*-2-cyclohexene-1,4-diol (**1b**)[7] as **I** and N-acyl-(S)-α-amino acyl group as **A**, and by successfully preparing optically pure PG intermediates[4] such as 2-oxabicyclo[3,3,0]oct-6-en-3-one (**2a**)[8] and 7-oxabicyclo[4,3,0]non-2-en-8-one (**2b**)[9] from separated **II** and **III**.

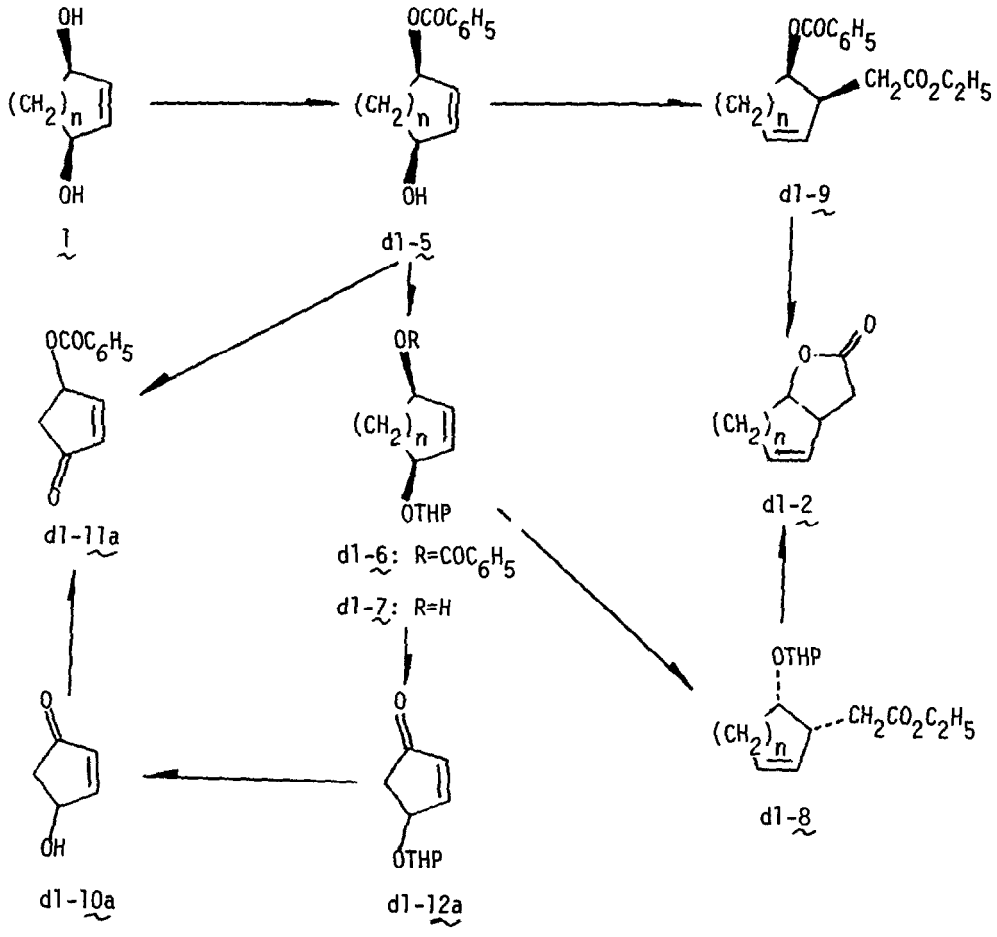
II. *Preparation of an enantiomeric pair of optically pure 2-oxabicyclo[3,3,0]oct-6-en-3-one((−)- and (+)-**2a**) from cis-cyclopentene-1,4-diol (**1a**)*

The acyl chlorides (**3**) of N-acyl-(S)-α-amino acids (**4**) were chosen as sources of optically active functional group (**A**) because of the availability and wide structural variations of **3** and anticipated superior crystallizability of N-acyl-(S)-α-amino acyl esters corresponding to **II** and **III**. Hence synthetic schemes to optically pure lactones (**2a**) were studied as shown in Scheme 2, by using *dl*-benzoate(*dl*-**5a**)[10] as a model compound of the monoester of **1a** which carries an N-acyl-(S)-α-amino acyl residue.

Introduction of the tetrahydropyranyl (THP) group into *dl*-**5a** prepared from **1a**, as a functional group which can be chemically discriminated from the acyl group (*vide supra*),[11] gave the THP ether (*dl*-**6a**) in 94% yield. The alcohol (*dl*-**7a**) obtained in 96% yield by hydrolysis of *dl*-**6a**, was subjected to the Claisen



Scheme 1.



a: n=1

b: n=2

Scheme 2.

rearrangement according to the report,[15,16] giving the rearrangement product (*dl*-**8a**). Alkaline hydrolysis of *dl*-**8a** followed by simultaneous cleavage of the THP group and lactonization, afforded *dl*-**2a** in 76% yield based on *dl*-**7a**.

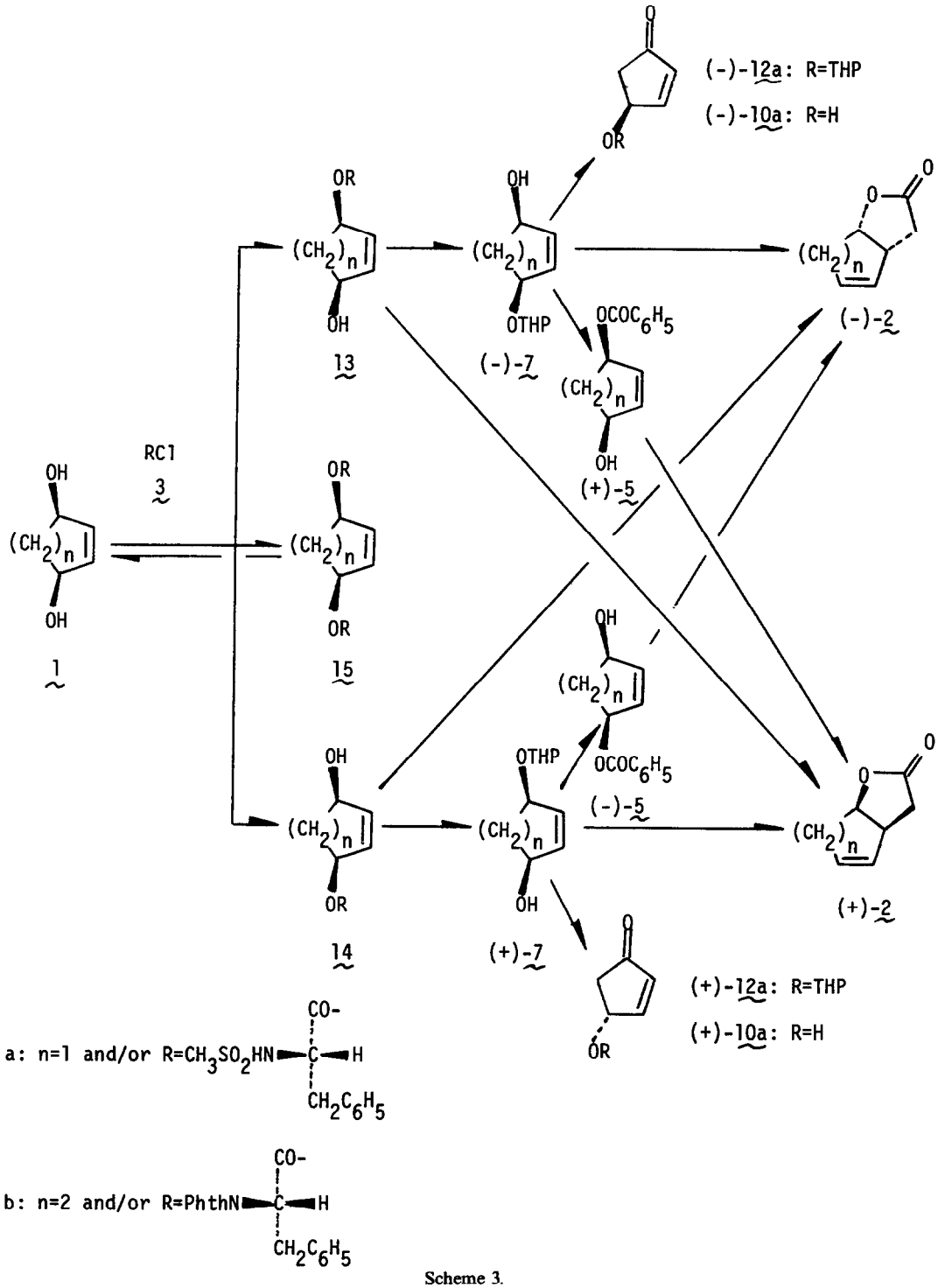
On the other hand, when *dl*-**5a** was directly treated under the conditions for the Claisen rearrangement,[15,16] the racemic lactone (*dl*-**2a**) could be obtained in 80% yield by way of *dl*-**9a**.

These results clearly disclose that if **1a** is monoacylated with **3** and the formed monoesters (**13** and **14**) (Scheme 3) are separated, the designed method should be realized. In order to evaluate which of the two reaction paths should be applied to two kinds of the monoesters (*vide infra*), it was necessary to determine the structures of these monoesters.[17] Therefore, the conversion of *dl*-**5a** to *dl*-4-hydroxy-2-cyclopentenone (*dl*-**10a**) was next attempted because the absolute configuration of optically active **10a** had been established.[18,19]

Although cleavage of the benzoyl group of *dl*-4-oxo-2-cyclo-pentenyl benzoate (*dl*-**11a**)[20] derived from *dl*-**5a**, was found to be fruitless,[21] *dl*-**10a** could be prepared from *dl*-**7a** by successive oxidation (81% yield) and acidic cleavage of the THP group (73% yield). The structure of *dl*-**10a** was confirmed by converting it into *dl*-**11a**.[20]

The preparation of the two diastereomeric monoesters (**13** and **14**) from **1a** and **3**, and their separation were next examined. After several unsuccessful attempts,[22] we found that N-mesyl-(S)-phenylalanyl chloride (**3a**) prepared from (S)-phenylalanine by successive mesylation (83% yield) and chlorination (91% yield), gave a superior result.

As shown in Scheme 3, reaction of **1a** with **3a** (1.0 eq) followed by purification with column chromatography, afforded the diester (**15a**), $[\alpha]_D^{20}$ − 51.3° ($CHCl_3$), and a mixture of the monoesters (**13a** and **14a**) in 24% and 51% yields. When the acylation of **1a** with **3a** (3.0 eq) was attempted in the presence of potassium bicarbonate (10 eq), **15a** and a mixture of **13a** and **14a** was obtained in 3,1% and 43% yields with a 40% recovery of **1a**. Separation of **13a** and **14a** was accomplished by successive trituration with ether and recrystallization, giving pure crystalline **13a**, $[\alpha]_D^{20}$ + 30.5° ($CHCl_3$), and crude **14a** (**13a**:**14a**



Scheme 3.

10–14:90–86),[23] $[\alpha]_D^{20}$ − 61.0° ($CHCl_3$), in 17% and 32% yields, respectively. Alkaline hydrolysis of useless **15a** readily recovered **1a** in 68% yield.

Before preparations of (−)- and (+)-**2a** were examined, the structures of **13a** and **14a** were determined by following the established scheme. Thus, successive tetrahydropyranylation of **13a** and hydrolysis gave (−)-**7a**, $[\alpha]_D^{20}$ − 20.3° ($CHCl_3$), in 81% overall yield. By similar treatment, **14a** was transformed to (+)-**7a**, $[\alpha]_D^{20}$ + 21.9° ($CHCl_3$), in 68% yield. When (−)- and (+)-**7a** were treated in a similar manner to that for *dl*-**7a**, (−)- and (+)-**10a**,[18,19] $[\alpha]_D^{20}$ − 94.1° ($CHCl_3$), 100% enantiomeric excess(ee),[24] and $[\alpha]_D^{20}$ + 67.0° ($CHCl_3$), 71% ee,[24] by way of (−)- and (+)-**12a** could be obtained.

As the structures of **13a** and **14a** were established, the preparation of (−)-**2a** was attempted as follows: the Claisen rearrangement[15,16] of (−)-**7a** followed by hydrolysis and lactonization as for *dl*-**7a**, gave (−)-**2a**,[26] $[\alpha]_D^{20}$ − 104° (MeOH), 100% ee,[27] in 80% yield

based on (−)-**7a**. On the other hand, when **14a** and the benzoate((−)-**5a**), $[\alpha]_D^{20}$ − 99.8° ($CHCl_3$), derived from (+)-**7a** in 78% yield, were subjected to the Claisen rearrangement[15,16] and the rearrangement products were hydrolyzed and lactonized similar to the preparations of *dl*-**2a** from *dl*-**5a**, two lots of partially optically active (−)-**2a**,[26] $[\alpha]_D^{20}$ − 84.0° (MeOH), 81% ee,[27] and $[\alpha]_D^{20}$ − 82.6° (MeOH), 79% ee,[27] were obtained in 40% and 88% yields, respectively. These partially optically active (−)-**2a** gave optically pure samples,[27] $[\alpha]_D^{20}$ − 104° (MeOH), on recrystallization.

When a reaction scheme similar to the preparation of (−)-**2a** was applied to (+)-**7a**, **13a**, and (+)-**5a**, $[\alpha]_D^{20}$ + 133° ($CHCl_3$), partially optically active (+)-**2a**,[26] $[\alpha]_D^{20}$ + 75.8° (MeOH), 73% ee,[27] was obtained from (+)-**7a**, and (+)-**2a**,[26] $[\alpha]_D^{20}$ + 103° (MeOH) and $[\alpha]_D^{20}$ + 104° (MeOH), 100% ee,[27] from **13a** and (+)-**5a**, respectively. Recrystallization of partially optically active (+)-**2a** also yielded (+)-**2a**, $[\alpha]_D^{20}$ + 104° (MeOH), 100% ee.[27]

While realization of our novel method was accomplished by the successful preparations of optically pure (−)- and (+)-**2a** from **1a** as mentioned above,[28] application of this concept to the synthesis of another important PG intermediate ((−)-**2b**) was further studied. This is a subject of the next section.

III. *Preparation of optically pure* (−)-7-*oxabicyclo*[4,3,0]*non*-2-*en*-8-*one*((−)-2b) *from* cis-2-*cyclohexene*-1,4-*diol* (**1b**)

Preliminary studies on the synthetic routes were carried out using the racemic benzoate (*dl*-**5b**) as a model compound of the two diastereomeric monoesters (**13** and **14**).

Treatment of *dl*-**5b** prepared from **1b**[7] in 45% yield, similar to that of *dl*-**5a**, gave *dl*-**2b**[9a] in 84% overall yield by way of *dl*-**9b**. On the other hand, when the THP ether (*dl*-**7b**) derived from *dl*-**5b** by way of *dl*-**6b** in 92% overall yield, was subjected to the Claisen rearrangement,[15,16] and the rearrangement product (*dl*-**8b**) was treated as in the preparation of *dl*-**2a** from *dl*-**7a**, *dl*-**2b**[9a] could be obtained in 74% yield based on *dl*-**7b**.

Since the scheme was established by using *dl*-**5b**, the preparation and separation of the two diastereomeric monoesters (**13** and **14**) was next undertaken. Several experiments using various types of **3**[29] revealed that N-phthaloyl-(S)-phenylanylchloride (**3b**)[30] was the most suitable optically active agent for monofunctionalization of **1b**.

Acylation of **1b**[7] with **3b**[30] (1.5 eq) in the presence of potassium bicarbonate (10 eq), followed by separation by a combination of column chromatography and recrystallization, afforded the crystalline diester (**15b**), $[\alpha]_D^{20}$ − 154° ($CHCl_3$), the crude monoester (**13b**) (**13b**: **14b** *ca* 3:1),[31] $[\alpha]_D^{20}$ − 75.3° ($CHCl_3$), and the other monoester (**14b**) (**13b**:**14b** *ca* 1:5),[31] $[\alpha]_D^{20}$ − 162° ($CHCl_3$), in 7.8%, 17% and 19% yields, respectively. Repeated recrystallizations of crude **13b** gave an almost pure sample (**13b**:**14b** *ca* 9:1)[31] showing $[\alpha]_D^{20}$ − 50.4° ($CHCl_3$). Alkaline hydrolysis of useless **15b** recovered **1b** in 88% yield.

When crude **13b** was subjected to a similar reaction scheme as for the preparation of *dl*-**2b** from *dl*-**5b**, partially optically active (+)-**2b**,[32] $[\alpha]_D^{20}$ + 15.2° (MeOH), 50% ee,[33] could be obtained in 86% overall yield. This revealed that the two diastereomers (**13b** and **14b**) had the structures shown in Scheme 3. Accordingly, the Claisen rearrangements[15,16] of both crude **14b** and crude (−)-**7b**, $[\alpha]_D^{20}$ − 17.3° ($CHCl_3$), prepared from crude **13b**, followed by successive treatments under hydrolytic and lactonization conditions, gave two sorts of (−)-**2b**,[32] $[\alpha]_D^{20}$ − 20.2° (MeOH), 67% ee,[33] and $[\alpha]_D^{20}$ − 15.0° (MeOH), 50% ee,[33] in 87% and 78% yields. Recrystallizations of these partially optically active samples yielded optically pure (−)-**2b**,[32] $[\alpha]_D^{20}$ − 30.0° (MeOH) and $[\alpha]_D^{20}$ − 29.8° (MeOH), in 53% and 34%[34] yields based on **14b** and **13b**.

As exemplified by the successful synthesis of optically pure (−)- and (+)-**2a** and (−)-**2b** from **1a, b** it is evident that our preparation of optically active compounds can be realized.

In the total synthesis of optically active complex molecules in which conventional chemical resolution of a racemic compound is employed, it has only been recognized that the resolution should be examined at an early stage in the synthetic scheme to save the amount of reagent and on the racemic intermediate which involves the functionality being convenient for the preparation of crystalline diasteromers. Thus, the synthetic scheme for constructing a frame work of a complex molecule has been designed, irrespective of the preparation of the optically active compound.

This research clearly discloses that a total amount of starting material can be converted to a desired optically active final product when the synthetic route proceeding through a *meso*-compound is selected and the preparation of optically active compound is attempted on the *meso*-compound. Namely, it is suggested that the synthetic route should be designed in combination with the preparation method for optically active compounds.

Applicability of our new concept was further studied by the successful synthesis of the steroid intermediate which is detailed in the accompanying paper.[35]

EXPERIMENTAL

All m.ps and b.ps are uncorrected. IR spectra were measured with a JASCO Spectrometer Model DS-403G and a JASCO IRA-1 Spectrometer. NMR spectra measurements were carried out using a Varian EM-360 Spectrometer. All signals are expressed by the ppm downfield from TMS used as an internal standard. Following abbreviations are used: singlet(s), doublet(d), triplet(t), quartet(q), multiplet(m), broad(br). Mass spectra were taken with a JMS D-100 Mass Spectrometer. Measurements of optical rotations were carried out using a Yanagimoto OR-10 Polarimeter. All reactions were performed using anhyd. solvents, and purifications by column chromatography were examined by the use of silica gel as an adsorvent except otherwise stated. The combined organic extracts obtained in each experiment were dried over Na_2SO_4 before successive filtration and evaporation *in vacuo*.

meso-2-*Cyclopetene*-1,4-*diol*(**1a**). This was prepared according to the reported method[7] as colorless prisms (recrystallized from petr. ether-acetone), mp 53–54.5° (lit.[7], mp 59–60°). This sample gave the corresponding crystalline di-*p*-nitrobenzoate, mp 193–194° (lit.,[7] mp 190–190.5°), and dibenzoate, mp 57–59.5° (lit.,[10] mp 58–60°).

dl-cis-4-*Hydroxy*-2-*cyclopentenyl benzoate*(dl-**5a**). Benzoyl chloride (5.0 g, 36 mmole) was added dropwise over 30 min to a soln of **1a** (5.0 g, 50 mmole) in pyridine (80 ml).[10] After being stirred at room temp overnight, the mixture was poured onto

ice water (300 ml). The *meso*-dibenzoate (1.3 g, 12%) which crystallized from the aqueous mixture, was collected by filtration and identified by spectral comparisons. The aqueous filtrate was extracted with ether, and the combined ethereal extracts were washed with H_2O. Filtration and evaporation *in vacuo* gave a residue, which was subjected to distillation, affording *dl*-**5a** as a colorless oil (4.1 g, 56%), bp 155° (2.5 mmHg). The oily product gradually solidified on standing, mp 50–53°. Recrystallization from hexane-ether gave an analytical sample of *dl*-**5a** as colorless prisms, mp 56.5–57.5°. IR ν_{max}^{KBr} cm^{-1}: 3380 (OH), 1715 (COO). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1730 (COO). NMR (in $CDCl_3$): 1.76 (1 H, dt, J = 15 and 4 Hz, one of $CH_2CH(OH)$), 2.71 (1 H, s, OH), 2.90 (1 H, dt, J = 15 and 7 Hz, one of $CH_2CH(OH)$), 4.75 (1 H, dd, J = 7 and 4 Hz, CH(OH)), 5.69 (1 H, dd, J = 7 and 4 Hz, CH(OCO)), 6.07 (2 H, m, CH=CH), 7.13–8.22 (5 H, m, C_6H_5). Mass: *m/e*: 204 [M^+], 106, 83. (Found: C, 70.65; H, 5.91. Calc. for $C_{12}H_{12}O_3$: C, 70.57; H, 5.92%).

dl-cis-4-*Tetrahydropyranoxy*-2-*cyclopentenol*(dl-**7a**)

(a) dl-cis-4-*Tetrahydropyranoxy*-2-*cyclopentenyl benzoate*(dl-**6a**). A THF soln (1.5 ml) of anhyd: TsOH (2.6 mg, catalytic amount) was added to a soln of *dl*-**5a** (0.30 g, 1.5 mmole) and dihydropyran (0.19 g, 2.3 mmole) in CH_2Cl_2 (10 ml), and the whole mixture was stirred at room temp for 2 hr. After quenching the reaction with a few drops of pyridine, the mixture was diluted with $CHCl_3$, and the organic soln was washed with H_2O. Filtration and evaporation *in vacuo* gave crude *dl*-**6a** as a colorless oil (0.40 g, 94%). IR ν_{max}^{film} cm^{-1}: 1716 (COO), 1113, 1070, 1025, 965 (THP). NMR (in $CDCl_3$): 1.1–2.5 (7 H, m, $CH_2CH_2CH_2CH_2CHO$ and one of CHCH(OCO)), 2.98 (1 H, ddt, J = 15, 7.5, and 2 Hz, one of $CH_2CH(OCO)$), 3.3–4.2 (2 H, m, OCH_2CH_2), 4.6–4.9 (2H, m, $OCHOCH_2CH_2$), 5.77 (1 H, dt, J = 7.5 and 5 Hz, CH(OCO)), 6.13 (2 H, m, CH=CH). This sample was immediately utilized for the next step.

(b) *Compound* dl-**7a**. A mixture of crude *dl*-**6a** (0.19 g, 0.66 mmole) and $Ba(OH)_2$-$8H_2O$ (0.13 g, 0.40 mmole) in MeOH (10 ml) was heated under reflux for 1.5 hr. After cooling, the mixture was extracted with ether, and the combined organic extracts were washed wth H_2O. Filtration and evaporation *in vacuo* gave crude *dl*-**7a** as a colorless oil (0.12 g, 96%). IR ν_{max}^{film} cm^{-1}: 3400 (OH), 1115, 1064, 1018, 968 (THP). NMR (in $CDCl_3$): 1.2–2.1 (7 H, m, $CH_2CH_2CH_2CH_2CHO$ and one of $CH_2CH(OH)$), 2.3–3.1 (1 H, m, one of $CH_2CH(OH)$), 3.3–4.3 (2 H, m, OCH_2CH_2), 4.4–4.9 (3 H, m, $OCHOCH_2CH_2$ and OH), 6.04 (2 H, s, CH=CH).

dl-2-*Oxabicyclo*[3,3,0]*oct*-6-*en*-3-*one*(dl-**2a**)

(a) *Preparation of* dl-**2a** *by the Claisen rearrangement of* dl-**5a**. A mixture of *dl*-**5a** (3.0 g, 15 mmole) and hydroquinone (0.1 g, catalytic amount) in triethyl orthoacetate (6.0 g, 37 mmole) was heated at 140° for 36 hr with continuous removal of the resulting EtOH.[15,16] After cooling, the mixture was extracted with EtOAc and the combined extracts were washed with H_2O. Filtration and evaporation *in vacuo* gave crude *dl*-**9a** as an oil (4.0 g, 97%), to which was added a soln of KOH (1.3 g, 23 mmole) in aq MeOH-(MeOH(50 ml)–H_2O(15 ml)). The methanolic soln was stirred at room temp overnight, then concentrated *in vacuo*. The residual mixture was acidified (pH ≒ 2) with HCl aq after being washed with EtOAc. The aq acidic soln was extracted with EtOAc. The combined extracts were kept at room temp overnight after addition of a THF soln (2.5 ml) of anhyd TsOH (4.3 mg, catalytic amount), and then they were washed with satd $NaHCO_3$aq. Filtration and evaporation *in vacuo* gave a residue which was purified by column chromatography(hexane-$CHCl_3$) to give pure *dl*-**2a** as a colorless oil (1.46 g, 80%), bp 74–76° (1 mmHg)(lit.,[15] bp 74° 0.3 mmHg); lit.,[36] bp 70–72° (0.2 mmHg)). Spectral (IR and NMR) properties of this sample were identical with those reported.[36]

In another experiment, crude *dl*-**9a** was purified by column chromatography(hexane-C_6H_6), giving pure *dl*-**9a** as an oil in 67% yield, bp 153–156° (1.5 mmHg). IR ν_{max}^{film} cm^{-1}: 1723 (COO). NMR (in $CDCl_3$): 1.12 (3 H, t, J = 7 Hz, CH_2CH_3), 2.3–3.0 (4 H, m, one of $CH_2CH(OCO)$ and $CHCH_2COO$), 3.2–3.8 (1 H, m, one of $CH_2CH(OCO)$), 4.06 (4 H, q, J = 7 Hz, CH_2CH_3), 5.6–6.0 (1 H, m, CHOCO), 5.77 (2 H, s, CH=CH). (Found: C, 70.31; H, 6.73. Calcd. for $C_{16}H_{18}O_4$: C, 70.05: H, 6.61%).

(b) *Preparation of* dl-**2a** *by the Claisen rearrangement of* dl-**7a**. Similar treatment of a mixture of *dl*-**7a** (0.45 g, 2.5 mmole) and hydroquinone (7 mg, catalytic amount) in triethyl orthoacetate (1.2 g, 7.4 mmole) gave after extraction an EtOAc soln of *dl*-**8a**. This was kept at room temp for 48 hr after the addition of TsOH-H_2O (catalytic amount). After washing with $NaHCO_3$aq, the organic soln was worked up in a manner similar to that for (a), giving pure *dl*-**2a** as a colorless oil (0.23 g, 76%) after purification with column chromatography ($CHCl_3$). This sample was identified by spectral (IR and NMR) comparisons.

When the EtOAc soln containing *dl*-**8a** was evaporated *in vacuo*, and the residue was purified by column chromatography (hexane-C_6H_6), pure *dl*-**8a** could be obtained as a colorless oil. IR ν_{max}^{film} cm^{-1}: 1735 (COO). NMR (in $CDCl_3$): 1.25 (3 H, t, J = 7.5 Hz, CH_2CH_3), 1.1–2.0 (6 H, m, $CH_2CH_2CH_2CH_2CHO$), 2.3–2.8 (4 H, m, one of $CH_2CH(OCO)$ and $CHCH_2COO$), 3.0–4.0 (3 H, m, OCH_2CH_2 and one of $CH_2CH(OCO)$), 4.12 (2 H, q, J = 7.5 Hz, CH_2CH_3), 4.3–4.7 (2 H, m, $OCHOCHCH_2$), 5.5–5.9 (2 H, m, CH=CH).

dl-4-*Oxo*-2-*cyclopentenyl benzoate*(dl-**11a**)

Jones reagent (1.84 ml, 4.9 mmole) was added to a stirred soln of *dl*-**5a** (1.00 g, 4.9 mmole) in acetone (10 ml) cooled in an ice bath. After stirring in the same cooling bath for 20 min, the mixture was diluted with ether and H_2O, and the upper organic layer was separated. The ethereal soln was washed successively with H_2O, satd $NaHCO_3$aq, and H_2O. Filtration and evaporation *in vacuo* gave crude *dl*-**11a** as a crystalline solid (1.0 g, 100%). Recrystallization from hexane-ether gave pure *dl*-**11a** as colorless plates (0.79 g, 79%), mp 87.5–88.5° (lit.,[20] mp 85°).

dl-4-*Hydroxy*-2-*cyclopentenone*(dl-**10**)

(a) dl-4-*Tetrahydropyranoxy*-2-*cyclopentenone*(dl-**12a**). Jones reagent (0.42 ml, 1.1 mmole) was added to a stirred soln of *dl*-**7a** (0.20 g, 1.1 mmole) in acetone (10 ml) cooled in a dry ice-CCl_4 bath, and the whole mixture was stirred in the same bath for 30 min. After the reaction was over, the mixture was diluted with EtOAc and the organic soln was washed successively with H_2O and satd. $NaHCO_3$aq. Filtration and evaporation *in vacuo* gave crude *dl*-**12a** as a colorless oil (0.16 g, 81%). IR ν_{max}^{film} cm^{-1}: 1725 (CO). NMR (in $CDCl_3$): 1.1–2.1 (6 H, m, $CH_2CH_2CH_2$), 2.1–3.1 (2 H, m, CH_2CO), 3.3–4.3 (2 H, m, CH_2O), 4.6–5.2 (2 H, m, $OCHOCHCH_2$), 6.30 (1 H, br d, J = 5 Hz, CH=CHCO), 7.58 (1 H, dt, J = 5 and 3 Hz, CHCH=CH). This sample was immediately used for the next hydrolysis.

(b) *Compound* dl-**10a**. An aq AcOH(AcOH(7 ml)–H_2O3 ml)) soln of *dl*-**12a** (0.94 g, 5.1 mmole) was stirred at room temp for 15 hr, and then was evaporated *in vacuo* after the addition of toluene. The residue was purified by column chromatography (first hexane, then $CHCl_3$), giving pure *dl*-**10a** as an oil (0.39 g, 73%), bp 90–92 (2 mmHg).[19] IR ν_{max}^{film} cm^{-1}: 3380 (OH), 1712 (CO). NMR (in $CDCl_3$): 2.21 (1 H, dd, J = 19 and 2 Hz, one of CH_2CO), 3.50 (1 H, br s, OH), 4.9–5.3 (1 H, m, CHO), 6.18 (1 H, dd, J = 6 and 1.5 Hz, CH=CHCO), 7.64 (1 H, dd, J = 6 and 2.5 Hz, CHC_=CH). Mass: *m/e*: 98 [M^+], 81, 70, 55, 42. Usual benzoylation of this material with benzoyl chloride in pyridine afforded *dl*-**11a**, mp 85.5–86.5°, which was identified by spectral comparisons.

(+)-N-*Mesyl*-(S)-*phenylalanyl chloride*(**3a**)

(a) (−)-N-*Mesyl*-(S)-*phenylalanine*(**4a**). To a stirred mixture of (S)-phenylalanine (50 g, 0.30 mole) and NaOH (15 g, 0.38 mole) in H_2O (300 ml) in an ice bath, was added dropwise mesyl chloride (42 g, 0.37 mole) over 30 min. During the addition of mesyl chloride, the mixture was kept weakly basic by adding NaOHaq. The stirring was continued for an additional 1 hr, and then the whole was washed with EtOAc and acidified (pH ≒ 2) with HClaq. The acidic mixture was extracted with EtOAc, and the combined extracts were washed with H_2O. Filtration and evaporation *in vacuo* gave crude **4a** (61.2 g, 83%), which was recrystallized from $CHCl_3$ to give pure **4a** as colorless needles, mp 105–107°, $[\alpha]_D^{20}$ − 16.7° (*c* = 4.2, $CHCl_3$). IR ν_{max}^{KBr} cm^{-1}: 3250 (NH), 1750, 1717 (COOH), 1394, 1317, 1149, 1114 (SO_2). NMR (in $CDCl_3$): 2.60 (3 H, s, CH_3), 3.10 (1 H, dd, J = 14 and 9 Hz, one of CH_2CH), 3.25 (1 H, dd, J = 14 and 5 Hz, one of CH_2CH), 4.2–4.7 (1 H, m, CH_2CH), 5.35 (1 H, d, J = 9 Hz, NH), 7.33 (5 H, s, C_6H_5), 8.3 (1 H, br s, COOH). (Found: C, 49.64; H, 5.35; N, 5.86. Calc for $C_{10}H_{13}NO_4S$: C, 49.37; C, 5.39; N, 5.76%). This acid also gave the crystalline dicyclohexylamine salt, mp 216–217.5° (recrystallized from MeOH), $[\alpha]_D^{20}$ − 15.5° (*c* = 1.34, AcOH). IR ν_{max}^{KBr} cm^{-1}: 1630 (COO^-). (Found: C, 62.23; H, 8.55; N, 6.60. Calc. for $C_{22}H_{36}N_2O_4S$: C, 62.20; H, 8.46; N, 6.55%).

(b) *Compound* **3a**. PCl_5 (27 g, 0.13 mole) was added to a suspension of **4a** (18.3 g, 0.075 mole) in benzene (200 ml) under stirring in an ice bath, and the mixture was stirred in an ice bath for 2 hr, then at room temp for 1 hr. After the insoluble material was removed by filtration, the filtrate was concentrated *in vacuo* to half the original volume. Addition of hexane to the benzene soln caused crystallization of crude **3a** as a fine powder (17.9 g, 91%), mp 84–85°. Recrystallization from hexane-ether gave pure **3a** as a pale yellow needles (16.8 g, 87%), mp 85–86°, $[\alpha]_D^{20}$ + 4.3° (*c* = 1.6, THF). IR ν_{max}^{KBr} cm^{-1}: 3260 (NH), 1792 (COCl), 1309, 1153 (SO_2). NMR (in $CDCl_3$): 2.64 (3 H, s, CH_3), 3.15 (1 H, dd, J = 14 and 8 Hz, one of CH_2CH), 3.30 (1 H, dd, J = 14 and 5 Hz, one of CH_2CH), 4.4–4.9 (1 H, m, CH_2CH), 5.5 (1 H, d, J = 9 Hz, NH), 7.30 (5 H, s, C_6H_5). This acid chloride (**3a**) was immediately used for the next acylation.

(+)-4(S)-*Hydroxy*-2-*cyclopenten*-1(R)-*yl* N-*mesyl*-(S)-*phenylalaninate*(**13a**), (−)-4(R)-*hydroxy*-2-*cyclopenten*-1(S)-yl N-*mesyl*-(S)-*phenylalaninate*(**14a**), *and* (−)-2-*cyclopenten*-1(R),4(S)-*diyl bis*-N-*Mesyl*-(S)-*phenylalaninate* (**15a**).

A THF soln (30 ml) of **3a** (10 g, 38 mmole) was added dropwise over 1 hr to a soln of **1a** (3.80 g, 38 mmole) in pyridine (150 ml) at room temp. After stirring at room temp overnight, the mixture was evaporated *in vacuo*, and the residue was dissolved in EtOAc. The organic soln was washed successively with satd $NaHCO_3$aq and H_2O. Filtration and evaporation *in vacuo* gave an oily residue, which was separated by column chromatography ($CHCl_3$) to give a mixture of **13a** and **14a** as an oil (6.4 g, 51%) and pure **15a** as an oil (5.0 g, 24%). Trituration of the mixture of **13a** and **14a** with ether gave crude **13a** as a crystalline solid (2.4 g, 19%). Recrystallization of crude **13a** from ether-$CHCl_3$ afforded pure **13a** (2.1 g, 17%) as colorless plates. Evaporation of the mother liquor from the trituration afforded crude **14a** as an oil (2.6 g, 32%) (**13a**:**14a** 10–14:90–86).[23] Three reaction products showed the following physical properties.

Compound **13a**, mp 118–119° and $[\alpha]_D^{20}$ + 30.5° (*c* = 2.5, $CHCl_3$). IR ν_{max}^{KBr} cm^{-1}: 3450 (OH), 3110 (NH), 1736 (COO). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1735 (COO). NMR (in $CDCl_3$): 1.67 (1 H, dt, J = 15 and 4 Hz, one of CH_2CHO), 2.32 (1 H, d, J = 8 Hz, OH), 2.70 (3 H, s, CH_3), 2.5–3.0 (1 H, m, one of CH_2CHO), 2.8–3.4 (2 H, m, $C_6H_5CH_2$), 4.2–4.6 (1 H, m, NCH), 4.5–5.0 (1 H, CHOH), 5.37 (1 H, d, J = 10 Hz, NH), 5.4–5.7 (1 H, m, CHOCO), 5.8–6.3 (2 H, m, CH=CH), 7.33 (5 H, s, C_6H_5). (Found: C, 55.50; H, 5.86; N, 4.22. Calc. for $C_{15}H_{19}NO_5S$: C, 55.37; H, 5.89; N, 4.31%).

Compound **14a** (**13a**:**14a** 10–14:90–86).[23] $[\alpha]_D^{20}$ − 61.0° (*c* = 2.4, $CHCl_3$). IR ν_{max}^{film} cm^{-1}: 3500 (OH), 3280 (NH), 1733 (COO). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1735 (COO). The NMR spectrum of this sample was similar to that of **13a**.

Compound **15a**: $[\alpha]_D^{20}$ − 51.3° (*c* = 1.7, $CHCl_3$). IR ν_{max}^{film} cm^{-1}: 3280 (NH), 1737 (COO). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1732 (COO). NMR (in $CDCl_3$): 1.93 (1 H, dt, J = 15 and 4 Hz, one of CH_2CHO). 2.70 (6 H, s, CH_3 × 2), 2.5–3.4 (5 H, m, one of CH_2CHO and $C_6H_5CH_2$×2), 4.2–4.7 (2 H, m, NCH×2), 5.68 (2 H, d, J = 9 Hz, NH×2), 5.5–5.9 (2 H, m, CHOCO×2), 6.25 (2 H, s, CH=CH), 7.37 (10 H, s, C_6H_5×2).

When the acylation was performed by vigorously stirring a mixture of **1a** (1.00 g, 10 mmole), **3a** (2.62 g, 30 mmole), and anhyd $KHCO_3$ (10 g, 100 mmole) in THF (100 ml) at room temp for 3.5 days, a mixture of **13a** and **14a** (1.39 g, 43%) and **15a** (0.17 g, 3.1%) could be obtained after successive filtration, evaporation, extraction with EtOAc, and separation by column chromatography as described above. A mixture of **13a** and **14a** could be separated into pure **13a** and crude **14a**. Physical properties of these products were identical with those described above. The $NaHCO_3$ soln obtained from the extraction of the reaction products, gave **4a** (1.52 g, 58% recovery), mp 105–106°, $[\alpha]_D^{20}$ − 16.9° (*c* = 4.3, $CHCl_3$), on re-extraction with EtOAc followed by evaporation *in vacuo*. Recovery of **1a** was performed by successive evaporation of the combined aq. phase produced by the extraction with EtOAc, purification by column chromatography (Al_2O_3, first $CHCl_3$, then ether), and distillation. Recovered **1a** weighed 0.40 g (40%) and showed bp 106° (1 mmHg) and mp 53–55°.

Recovery of **1a** from **15a** was performed as follows. A mixture of **15a** (2.25 g, 4.1 mmole) and $Ba(OH)_2$-$8H_2O$ (2.0 g, 6.3 mmole) in aq. MeOH(MeOH(25 ml)-H_2O(5 ml)) was kept at room temp for 4 hr, and then evaporated *in vacuo*. Water (25 ml) was added to the residue, and the aq mixture was washed with EtOAc. After CO_2 gas was bubbled through the aq mixture, the whole was evaporated *in vacuo*. The residue was extracted with $CHCl_3$, and the combined $CHCl_3$ extracts were evaporated *in vacuo*, affording **1a** (0.28 g, 68%), bp 108° (1.5 mmHg) and mp 53–54°. HClaq was added to the material being insoluble to $CHCl_3$, and the acidic soln was extracted with EtOAc. The combined extracts were washed with H_2O. Filtration and evaporation *in vacuo*, followed by recrystallization from $CHCl_3$, gave **4a** as colorless needles (1.3 g, 65%), mp 105–106° and $[\alpha]_D^{20}$ − 16.4° (*c* = 4.1, $CHCl_3$).

(−)-4(S)-*Tetrahydropyranoxy*-2(R)-*cyclopentenol*((−)-**7a**) *and Its* (+)-4(R),2(S)-*Isomer*((+)-**7a**)

(a) *Compound* (−)-**7a** *from* **13a**. Similar treatment of **13a** (mp 118–119°, $[\alpha]_D^{20}$ + 30.5° (*c* = 2.5, $CHCl_3$)) (6.50 g, 20 mmole) as for the preparation of *dl*-**7a** from *dl*-**5a** gave crude (+)-4(S)-tetrahydropyranoxy-2-cyclopenten-1(R)-yl N-mesyl-(S)-phenylalaninate as an oil (8.16 g, 100%), $[\alpha]_D^{20}$ + 12.7° (*c* = 2.6, MeOH). IR ν_{max}^{film} cm^{-1}: 3270 (NH). 1735 (COO).

The crude oil was dissolved in aq THF(THF(80 ml)-H_2O(30 ml)) containing NaOH (1.2 g, 30 mmole), and the mixture was stirred at room temp for 5 hr. After evaporation *in vacuo*, the residue was dissolved in ether, and the ethereal soln was washed with H_2O. Filtration and evaporation *in vacuo* gave crude (−)-**7a** as an oil (3.9 g). This was purified by column chromatography ($CHCl_3$), giving pure (−)-**7a**[37] as a colorless oil (3.0 g, 81% based on **13a**). $[\alpha]_D^{20}$ − 20.3° (*c* = 1.3, $CHCl_3$).

The aq alkaline soln obtained by extraction with ether was acidified with HClaq and extracted with EtOAc. The combined extracts were washed with H_2O. Filtration and evaporation *in vacuo* recovered **4a** as a crystalline solid (3.5 g, 72%), mp 105–107°, $[\alpha]_D^{20}$ − 16.0° (*c* = 4.1, $CHCl_3$).

(b) *Compound* (+)-**7a** *from* **14a**. Similar treatment of crude **14a** ($[\alpha]_D^{20}$ − 61.0° (*c* = 2.4, $CHCl_3$)) (1.36 g, 4.2 mmole) afforded (+)-**7a**[37] as a colorless oil (0.52 g, 68% based on **14a**), $[\alpha]_D^{20}$ + 21.9° (*c* = 1.3, $CHCl_3$), by way of (−)-4(R)-tetrahydropyranoxy-2-cyclopenten-1(S)-yl N-mesyl-(S')-

phenylalaninate (1.72 g, quantitative yield), $[\alpha]_D^{20}$ − 26.8° (*c* = 2.8, MeOH).

(−)-4(S)-*Hydroxy*-2-*cyclopentenone*((−)-**10a**) *and its* (+)-4(R)-*isomer*((+)-**10a**)

(a) *Compound* (−)-**10a**. Oxidation of (−)-**7a** ($[\alpha]_D^{20}$ − 20.7° (*c* = 1.3, $CHCl_3$)) (3.0 g, 16 mmole) as for *dl*-**7a** gave (−)-**12a**[37] as a colorless oil (2.5 g, 83%), $[\alpha]_D^{20}$ − 70.5° (*c* = 1.3, $CHCl_3$). Similar treatment of (−)-**12a** (1.00 g, 5.5 mmole) to that for dl-**12a** afforded (−)-**10a**[18,19,37] as colorless oil (0.47 g, 87%), bp 83° (0.7 mmHg), $[\alpha]_D^{20}$ − 94.1° (*c* = 3.4, $CHCl_3$), 100% ee.[24] (Found: C, 60.81; H, 6.25. Calc for $C_5H_6O_2$: C, 61.21; H, 6.17%).

(b) *Compound* (+)-**10b**. The alcohol ((+)-**7a**) ($[\alpha]_D^{20}$ + 21.9 (*c* = 1.3, $CHCl_3$)) (0.52 g, 2.8 mmole) was oxidized as for (−)-**7a** and gave (+)-**12a**[37] as a colorless oil (0.41 g, 80%), $[\alpha]_D^{20}$ + 67.0° (*c* = 1.6, $CHCl_3$). Cleavage of the THP group of (+)-**12a** (0.41 g, 2.3 mmole) gave (+)-**10a**[18,19,37] as a colorless oil (0.17 g, 77%), bp 88–91° (0.9 mmHg), $[\alpha]_D^{20}$ + 77.3° (*c* = 1.6, $CHCl_3$), 84% ee.[24]

(+)-4(S)-*Hydroxy*-2-*cyclopenten*-1(R)-yl *benzoate*((+)-**5a**) *and its* (−)-4(R),1(S)-*isomer*((−)-**5a**

(a) *Compound* (+)-**5a**. A CH_2Cl_2 soln (20 ml) of benzoyl chloride (1.30 g, 9.2 mmole) was added to a stirred soln of (−)-**7a** ($[\alpha]_D^{20}$ − 20.3° (*c* = 1.3, $CHCl_3$)) (1.13 g, 6.1 mmole) and pyridine (2 ml) in CH_2Cl_2 (20 ml) over 30 min, and the whole mixture was heated under reflux with stirring for 15 hr. After cooling, the mixture was washed successively with HClaq. $NaHCO_3$aq, and H_2O. Filtration and evaporation *in vacuo* gave an oily residue to which was added cold aq AcOH(AcOH:H_2O 7:3) (100 ml) containing pyridine (1 ml). After being kept at room temp overnight, the mixture was evaporated *in vacuo*. The residue was disolved in AcOEt, and the soln was washed successively with H_2O and satd $NaHCO_3$ aq. The residue obtained by filtration and evaporation *in vacuo* was purified by column chromatography ($CHCl_3$), giving pure (+)-**5a** as an oil (1.06 g, 85%), bp 143–146° (0.15 mmHg), $[\alpha]_D^{20}$ + 130° (*c* = 2.3, $CHCl_3$). The alcohol ((+)-**5a**) which gradually solidified on standing, was recrystallized from hexane-ether to give colorless needles[37] showing mp 62–63° and $[\alpha]_D^{20}$ + 133° (*c* = 1.7, $CHCl_3$).

(b) *Compound* (−)-**5a**. Treatment of (+)-**7a**($[\alpha]_D^{20}$ + 21.9° (*c* = 1.3, $CHCl_3$)) (0.52 g, 2.8 mmole) as described in (a) gave (−)-**5a**[37] as an oil (0.45 g, 78%), $[\alpha]_D^{20}$ − 99.8° (*c* = 2.0, $CHCl_3$).

(−)-1(S),5(R)-2-*Oxabicyclo*[3,3,0]*oct*-6-*en*-3-*one*((−)-**2a**)

(a) *Preparation of* (−)-**2a** *by the Claisen rearrangement of* (−)-**7a**. Treatment of (−)-**7a**($[\alpha]_D^{20}$ − 20.3° (*c* = 1.3, $CHCl_3$)) (1.3 g, 7.1 mmole) similar to that of *dl*-**7a** gave (−)-**2a**[26] as a solid (0.70 g, 80%) after purification by column chromatography ($CHCl_3$). This sample showed bp 73–76° (1 mmHg) and $[\alpha]_D^{20}$ − 104° (*c* = 1.1, MeOH), and gradually solidified on standing at room temp. Recrystallization from hexane-ether gave pure (−)-**2a**[26,37] as colorless needles, mp 45–46°, $[\alpha]_D^{20}$ − 104° (*c* = 1.1, MeOH), 100% ee.[27]

(b) *Preparation of* (−)-**2a** *by the Claisen rearrangement of* **14a**. The monoester (**14a**) ($[\alpha]_D^{20}$ − 59.9° (*c* = 1.7, $CHCl_3$)) (2.36 g, 7.2 mmole) was treated as for the Claisen rearrangement of *dl*-**5a**, giving (−)-**2a**[26] as an oil (0.36 g, 40%) after purification by column chromatography ($CHCl_3$). This sample showed bp 72–75° (0.5 mmHg) and $[\alpha]_D^{20}$ − 84.0° (*c* = 1.3, MeOH), 81% ee.[27] Recrystallization of the solidified distillate from hexane-ether afforded (−)-**2a**[26,37] as colorless needles in 72% recovery, mp 45–46° and $[\alpha]_D^{20}$ − 105° (*c* = 1.0, MeOH), 100% ee.[27]

(c) *Preparation of* (−)-**2a** *by the Claisen rearrangement of* (−)-**5a**. Similar treatment of (−)-**5a** ($[\alpha]_D^{20}$ − 99.8° (*c* = 2.0, $CHCl_3$)) (0.66 g, 3.2 mmole) gave (−)-**2a**[26] as a solid (0.35 g, 88%) after purification by column chromatography ($CHCl_3$), bp 83–86° (1 mmHg) and $[\alpha]_D^{20}$ − 82.6° (*c* = 1.2, MeOH), 79% ee.[27] Recrystallization of this sample from hexane-ether gave (−)-**2a**[26,37] as colorless needles in 66% recovery, mp 45–46° and $[\alpha]_D^{20}$ − 104° (*c* = 1.2, MeOH), 100% ee.[27]

(+)-1(R),5(S)-2-*Oxabicyclo*[3,3,0]*oct*-6-*en*-3-*one*((+)-**2a**,

(a) *Preparation of* (+)-**2a** *by the Claisen rearrangement of* (+)-**7a**. Treatment of (+)-**7a**($[\alpha]_D^{20}$ + 16° (*c* = 1.5, $CHCl_3$)[38] (1.15 g, 6.3 mmole) as for the preparation of *dl*-**2a** from *dl*-**7a**, gave (+)-**2a**[26] as a semisolid (0.56 g, 72%), $[\alpha]_D^{20}$ + 75.8° (*c* = 1.0, MeOH), 73% ee.[27] This sample was recrystallized from hexane-ether, giving (+)-**2a**[26,37] as colorless needles in 68% recovery, mp 44.5–46° and $[\alpha]_D^{20}$ + 104° (*c* = 1.2, MeOH), 100% ee.[27]

(b) *Preparation of* (+)-**2a** *by the Claisen rearrangement of* **13a**. The monoester **13a** ($[\alpha]_D^{20}$ + 29.7° (*c* = 2.0, $CHCl_3$)) (2.9 g, 8.9 mmole) was treated as for *dl*-**5a** to give (+)-**2a**[26] as a solid (0.59 g, 53%), bp 70–73° (0.5 mmHg), mp 44°, and $[\alpha]_D^{20}$ + 104° (*c* = 1.1, MeOH), 100% ee.[27] Recrystallization from hexane-ether gave (+)-**2a**[26,37] as colorless needles, mp 45.4–46.5° and $[\alpha]_D^{20}$ + 103° (*c* = 0.9, MeOH), 100% ee.[27]

(c) *Preparation of* (+)-**2a** *by the Claisen rearrangement of* (+)-**5a**. Similar treatment of (+)-**5a** ($[\alpha]_D^{20}$ + 130° (*c* = 2.3, $CHCl_3$)) (0.66 g, 3.2 mmole) gave (+)-**2a**[26,37] as colorless needles (0.36 g, 90%), bp 82–85° (0.9 mmHg), mp 45–46°, and $[\alpha]_D^{20}$ + 104° (*c* = 1.3, MeOH), 100% ee.[27]

meso-2-*Cyclohexene*-1,4-*diol* (**1b**). This compound was prepared according to the reported method,[7] mp 57–59 (lit.,[7] 59–60°).

dl-cis-4-*Hydroxy*-2-*cyclohexenyl benzoate* (dl-**5b**). The *meso*-diol (**1b**) (2.30 g, 20 mmole) was treated according to the preparation of *dl*-**5a** to give a crude mixture of products as an oil after evaporation of the ethereal extract. Purification by column chromatography ($CHCl_3$) gave *meso*-2-cyclohexen-1,4-diyl bisbenzoate as a solid (0.96 g, 15%) and *dl*-**2b** as an oil (1.97 g, 45%). These samples showed the following physical properties.

meso-2-*Cyclohexen*-1,4-*diyl bisbenzoate*. Colorless prisms (recrystallized from hexane), mp 83–84°. IR ν_{max}^{KBr} cm^{-1}: 1705 (COO). NMR (in $CDCl_3$): 2.0–2.3 (4 H, m, CH_2CH_2), 5.52 (2 H, br s, CHOx2), 6.07 (2 H, s, CH=CH), 7.2–8.3 (10 H, m, C_6H_5x2). Mass: *m/e*: 322 [M^+]. (Found: C, 74.40; H, 5.64. Calc for $C_{20}H_{18}O_4$: C, 74.52; H, 5.63%).

Compound dl-**2b**, bp 140–144° (2 mmHg). IR ν_{max}^{film} cm^{-1}: 3400 (OH), 1715 (COO). NMR (in $CDCl_3$): 1.8–2.3 (4 H, m, CH_2CH_2), 2.93 (1 H, s, OH), 4.25 (1 H, m, CHOH), 5.50 (1 H, m, CHOCO), 5.99 (2 H, m, CH=CH), 7.2–8.3 (5 H, m, C_6H_5). Mass: m/e: 218 [M^+]. (Found: C, 71.82; H, 6.43. Calc for $C_{13}H_{14}O_3$: C, 71.54; H, 6.47).

dl-cis-4-*Tetrahydropyranoxy*-2-*cyclohexenol*(dl-**7b**)

(a) *Compound* dl-**6b**. Treatment of *dl*-**5b** (0.40 g, 1.8 mmole) as for the preparation of *dl*-**6a** gave *dl*-**6b** as an oil (0.54 g, 98%) after evaporation of the organic extract. IR ν_{max}^{film} cm^{-1}: 1715 (COO). NMR (in $CDCl_3$): 1.2–2.4 (10 H, m, CH_2CH_2 and $CH_2CH_2CH_2CH_2CHO$), 3.3–4.4 (3 H, m, CH_2O and $CHOCHO$), 4.76 (1 H, br s, $OCHO$), 5.43 (1 H, br s, CHOCO), 6.00 (2 H, m, CH=CH), 7.2–8.3 (5 H, m, C_6H_5).

(b) *Compound* dl-**7b**. Similar to the preparation of *dl*-**7a**, hydrolysis of *dl*-**6b** (0.54 g, 1.8 mmole) with KOH (0.15 g, 2.7 mmole) in MeOH gave *dl*-**7b** as a colorless oil (0.33 g, 92%). IR ν_{max}^{film} cm^{-1}: 3380 (OH). NMR (in $CDCl_3$): 1.1–2.1 (10 H, m, CH_2CH_2 and $CH_2CH_2CH_2CH_2CHO$), 3.2–4.5 (5 H, m, OH, CH_2O, CHOCHO, and CHOH), 4.70 (1 H, br s, $OCHO$), 5.94 (2 H, s CH=CH).

dl-7-*Oxabicyclo*[4,3,0]*non*-2-*en*-8-*one*(dl-**2b**)

(a) *Preparation of dl*-**2b** *by the Claisen rearrangement of* dl-**5b**. A mixture of *dl*-**5b** (0.40 g, 1.8 mmole) was treated as for the preparation of *dl*-**2a** from *dl*-**5a**, giving the rearrangement product (*dl*-**9b**) as a colorless oil (0.49 g, 93%), bp 160° (1 mmHg). IR ν_{max}^{film} cm^{-1}: 1725 (COO). NMR (in $CDCl_3$): 1.21 (3 H, t, J = 7 Hz, CH_2CH_3), 1.7–2.5 (6 H, m, CH_2CH_2 and CH_2COO), 3.10 (1 H, m, $CHCH_2COO$), 4.05 (2 H, q, J = 7 Hz, CH_2CH_3), 5.3–6.1 (3 H, m, CHOCO and CH=CH), 7.2–8.2 (5 H, m, C_6H_5). Mass: m/e 288 [M^+].

(Found: C, 71.00; H, 7.03. Calc. for $C_{17}H_{20}O_4$: C, 70.81; H, 6.99%).

Hydrolysis of *dl*-**9b** (0.44 g, 1.5 mmole) with KOH (0.30 g, 5.4 mmole) in aq MeOH(MeOH(10 ml)-H_2O(2 ml)) followed by acidic work-up as for the preparation of *dl*-**2a** from *dl*-**5a**, gave *dl*-**2b** as a colorless oil (0.19 g, 90%), bp 94–96° (4 mmHg) (lit.,[9b] bp 85–90° (22 mmHg); lit.,[15] bp 78° (0.16 mmHg)).

(b) *Preparation of dl-***2b** *by the Claisen rearrangement of dl-***7b**. Treatment of *dl*-**7b** (0.41 g, 2.1 mmole) as for the preparation of *dl*-**2a** from *dl*-**7a** gave the crude rearrangement product (*dl*-**8b**) after evaporation of the EtOAc extract. This was subjected to the alkaline hydrolysis as described in (a). The product was dissolved in aq AcOH(AcOH(3.5 ml)-H_2O (1.5 ml)), and the aq acidic soln was kept at room temp for 2 days. Evaporation *in vacuo*, followed by usual isolation with EtOAc, gave *dl*-**2b** (0.21 g, 74% based on *dl*-**7b**) as an oil. Spectral (IR and NMR) properties of this sample were identical with those of the sample obtained in (a).

(−)-4(S)-*Hydroxy*-2-*cyclohexen*-1(R)-yl N-*phthaloyl*-(S)-*phenylalaninate* (**13b**), (−)-4(R)-*hydroxy*-2-*cyclohexen*-1(S)-yl N-*phthaloyl*-(*S*)-*phenylalaninate* (**14b**), *and* (−)-2-*cyclohexen*-1(R),4(S)-*diyl bis*-N-*phthaloyl*-(S)-*phenylalaninate* (**15b**)

A THF soln (40 ml) of **3b**[30] (14.1 g, 45 mmole) was added over 2 hr to a cooled (9–10°) suspension containing **1b** (3.42 g, 30 mmole) and $KHCO_3$ (30 g, 0.30 mole) in THF (50 ml) under vigorous stirring. After the stirring was continued at room temp for 4.5 days, the insoluble inorganic salts were removed by filtration, and was washed with ether. The combined filtrates were washed with H_2O. Filtration and evaporation *in vacuo* gave the oily residue which was subjected to column chromatography ($CHCl_3$), giving **15b** as colorless needles (1.56 g, 7.8%), mp 182.5–183° (recrystallized from EtOAc), $[\alpha]_D^{20}$ − 154° (*c* = 1.2, $CHCl_3$), and a mixture of **13b** and **14b** as a semisolid (6.29 g, 54%), $[\alpha]_D^{20}$ − 124° (*c* = 1.8, $CHCl_3$). The mixture of **13b** and **14b** was dissolved in ether, and the soln was cooled in an ice bath. This operation yielded a mixture of **13b** and **14b** as colorless needles (4.02 g, 34%) in which **13b** was predominant, mp 94–98°, $[\alpha]_D^{20}$ − 106° (*c* = 1.5, $CHCl_3$). Further recrystallization of this sample from ether afforded crude **13b** (**13b**:**14b** *ca* 3:1[31]) as colorless needles (1.97 g, 17%), mp 97.5–100°, $[\alpha]_D^{20}$ − 75.3° (*c* = 1.1, $CHCl_3$). Repeated recrystallization of this material from ether gave almost pure **13b** (**13b**:**14b** *ca* 9:1[31]) as colorless needles which exhibited the constant mp and optical rotation, mp 105.5–106.5°, $[\alpha]_D^{20}$ − 50.4° (*c* = 1.8, $CHCl_3$). Concentration of the original ethereal mother liquor gave crude **14b** (**13b**:**14b** *ca* 1:5[31]) as colorless needles (2.16 g, 19%), mp 69–71°, $[\alpha]_D^{20}$ − 162° (*c* = 1.3, $CHCl_3$).

Separated reaction products showed the following spectral properties.

Compound **15b**: IR ν_{max}^{KBr} cm^{-1}: 1777, 1743, 1715 (CONCO and COO). NMR (in $CDCl_3$): 1.7–2.0 (4 H, m, CH_2CH_2), 3.49 (4 H, d, J = 9 Hz, C_6H_5CHX2), 5.0–5.5 (4 H, m, CHCOOx2 and CHOCOx2), 5.87 (2 H, s, CH=CH), 7.1–7.9 (18 H, m, C_6H_4 × 2 and C_6H_5 × 2). (Found: C, 71.66; H, 4.98; N, 4.05. Calc for $C_{40}H_{32}O_8N_2$: C, 71.85; H, 4.82; N, 4.19%).

Compound **13b** (**13b**:**14b** *ca* 9:1[31]): IR ν_{max}^{KBr} cm^{-1}: 3250 (OH), 1775, 1738, 1713 (CONCO and COO). NMR (in $CDCl_3$): 1.7–2.3 (5 H, m, CH_2CH_2 and OH), 3.4–3.8 (2 H, m, $C_6H_5CH_2$), 4.2 (1 H, br s, CHOH), 5.1–5.4 (1 H, m, CHCOO), 5.35 (1 H, br s, CHOCO), 5.9 (2 H, m, CH=CH), 7.1–7.9 (9H, m, C_6H_4 and C_6H_5). (Found: C, 70.54; H, 5.43; N, 3.54. Calc for $C_{23}H_{21}O_5N$: C, 70.58; H, 5.41; N, 3.58%).

Compound **14b** (**13b**:**14b** *ca* 1:5[31]): IR ν_{max}^{KBr} cm^{-1}: 3250 (OH), 1776, 1735, 1715 (CONCO and COO). NMR spectrum of this sample were quite similar to that of **13b**.

Recovery of **1b** from **15b** (1.34 g, 2 mmole) was carried out as in the case of **15a**, giving crude **1b** (0.20 g, 88%) after purification by column chromatography (Al_2O_3, first $CHCl_3$, then ether).

(+)-1(S),6(R)-7-*Oxabicyclo*[4,3,0]*non*-2-*en*-8-*one*((+)-**2b**)

Treatment of **13b** (**13b**:**14b** *ca* 3:1[31]) ($[\alpha]_D^{20}$ − 75.3° (*c* = 1.1, $CHCl_3$)) (1.17 g, 3.0 mmole) as for the preparation of *dl*-**2b** from *dl*-**5b**, gave (+)-**2b**[32] as a colorless semi-solid (0.35 g, 86%) after purification by column chromatography ($CHCl_3$), bp 95–97° (4 mmHg), $[\alpha]_D^{20}$ + 15.2 (*c* = 1.3, MeOH), 50% ee.[33] Recrystallization from hexane-ether gave pure (+)-**2b**[32,37] as colorless prisms (0.15 g, 36% based on **13b**), mp 68–69°, $[\alpha]_D^{20}$ + 30.0° (*c* = 1.1, MeOH), 100% ee.[33]

(−)-1(R),6(S)-7-*Oxabicyclo*[4,3,0]*non*-2-*en*-8-*one*((−)-**2b**)

(a) Treatment of **13b** (**13b**:**14b** *ca* 3:1[31]) ($[\alpha]_D^{20}$ − 75.3° (*c* = 1.1, MeOH)) (1.17 g, 3.0 mmole) as for the preparation of *dl*-**7b** from *dl*-**5b** gave (−)-**7b**[37] as an oil (0.59 g, 100%), $[\alpha]_D^{20}$ − 17.3° (*c* = 1.2, $CHCl_3$). The alcohol ((−)-**7b**) was directly treated as *dl*-**7b**, giving (−)-**2b**[32] as a semisolid (0.32 g, 78% based on **13b**), bp 96–97° (4 mmHg), $[\alpha]_D^{20}$ − 15.0° (*c* = 1.3, MeOH), 50% ee.[33] This was twice recrystallized from hexane-ether to give pure (−)-**2b**[32,37] as colorless prisms (0.14 g, 34% based on **13b**), mp 68.5–69.5°, $[\alpha]_D^{20}$ − 29.8° (*c* = 0.9, MeOH), 100% ee.[33]

When **13b** (**13b**:**14b** *ca* 9:1[31]) (1.17 g, 3.0 mmole) showing $[\alpha]_D^{20}$ − 50.4° (*c* = 1.2, $CHCl_3$) was subjected to the same reaction scheme as that described above, (−)-**2b**[32] (0.33 g, 80% based on **13b**), mp 59–60°, $[\alpha]_D^{20}$ − 23.5° (*c* = 1.0, MeOH), 78% ee,[33] could be obtained by way of (−)-**7b**,[37] $[\alpha]_D^{20}$ − 26.2° (*c* = 1.1, $CHCl_3$). Recrystallization of this sample from hexane-ether afforded pure (−)-**2b**[32,37] as colorless needles (0.24 g, 58% based on **13b**), mp 68.5–69.5°, $[\alpha]_D^{20}$ − 30.1° (*c* = 1.1, MeOH), 100% ee.[33]

(b) *Preparation of* (−)-**2b** *by the Claisen rearrangement of* **14b**: Similar treatment of **14b** (**13b**:**14b** *ca* 1:5[31]) ($[\alpha]_D^{20}$ − 162° (*c* = 1.3, $CHCl_3$)) (1.17 g, 3.0 mmole) as for the preparation of *dl*-**2b** from *dl*-**5b** gave (−)-**2b** as a semisolid (0.36 g, 87% based on **14b**), $[\alpha]_D^{20}$ − 20.2° (*c* = 1.2, MeOH), 67% ee.[33] Recrystalization of this sample from hexane-ether gave pure (−)-**2b**[32,37] as colorless prisms (0.22 g, 53% based on **14b**), mp 68–69.5°, $[\alpha]_D^{20}$ − 30.0° (*c* = 1.0, MeOH), 100% ee.[33]

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[21]Hydrolysis with wheat germ lipase which was reported to give *dl*-**10a** from the 4-acetoxy analogue of *dl*-**11a**,[19] was not attempted on *dl*-**11a**.

[22]Prior to the use of **3a**, N-tosyl-(S)-prolyl chloride and **3b**[30] were employed as sources of **A**. However, separation of the monoesters derived from N-tosyl-(S)-prolyl chloride, was only possible by preparative tlc and the separated monoesters obtained from **3b** would not crystallize.

[23]Since crude **14a** afforded (−)- and (+)-**2a** being 73–81% optically active, it became evident that crude **14a** involved **13a** and **14a** in a ratio of 10–14 to 90–86.

[24]Although there had been reported that the samples of (+)-**10a** showing $[\alpha]_D^{28}$ + 81° ($CHCl_3$) and $[\alpha]_D^{20}$ + 59° (c = 0.063, MeOH) were 100%[18] and 90%[19] ee, we adopted $[\alpha]_D^{20}$ − 94.1° (c = 3.4, $CHCl_3$) as the optical rotation of optically pure (−)-**10a** because (−)-**7a** which had given the above mentioned (−)-**10a**, afforded optically pure (−)-**2a**. Recently, Rikards, *et al.*[25] also reported the similar lower optical rotation for optically pure (+)-**10a**, $[\alpha]_D^{22}$ + 81° ($c = 1.12 \times 10^{-2}$, $CHCl_3$) and $[\alpha]_D^{20}$ + 96° ($c = 1.18 \times 10^{-1}$, MeOH).

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[26]The absolute configurations of (−)- and (+)-**2a** are established in ref. 8*b* and 8*g*.

[27]Optically pure (−)-**2a** prepared by the asymmetric synthesis[8b] had been reported to have mp 46–47° and $[\alpha]_D^{25}$ − 106° (c = 1, MeOH). However, we assumed that (−)-**2a** showing mp 45–46° and $[\alpha]_D^{20}$ − 104° (c = 1.1, MeOH), was 100% ee because the repeated recrystallizations of this sample did not increase its mp and optical rotation.

[28]Optically pure (−)-**2a** was further converted to another important PG intermediate, (−)-7(R)-hydroxy-6(R)-hydroxymethyl-1(S),5(R)-2-oxabicyclo[3,3,0]octan-3-one, mp 116–117.5° and $[\alpha]_D^{20}$ − 43.9° (c = 1.2, MeOH) (lit.,[8d] mp 117.5–118.5° and $[\alpha]_D^{20}$ − 43.4° (c = 1.46, MeOH)), following to the method reported by Kovács, *et al.*[8d]

[29]In addition to **3b**, N-tosyl-(S)-phenylalanyl chloride, N-tosyl-(S)-alanyl chloride, and **3a** were examined as reagents for monofunctionalization of **1b**.

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[31]This ratio was calculated based on the optical purity of (−)- and (+)-**2b** obtained from this sample.

[32]The absolute configurations of (−)- and (+)-**2b** are established in Ref. 9*c*.

[33]Although (−)-**2b**, $[\alpha]_D^{27}$ − 28° (c = 0.83, MeOH), prepared by the chemical resolution, had been reported to be optically pure,[9c] we assumed that (−)-**2b** showing the higher rotation, $[\alpha]_D^{20}$ − 30.1° (c = 1.1, MeOH), was optically pure.

[34]This was erroneously reported as 53% in the preliminary communication (Ref. 2).

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[37]This sample showed identical spectral (IR and NMR) and chromatographic (tlc) properties with those of the corresponding racemic compound.

[38]This was erroneously reported as $[\alpha]_D^{20}$ + 16° (c = 1.5, MeOH) in the preliminary communication (ref. 2).