Organic Process Research & Development **2006**, *10,* 500–504

Improved Practical Asymmetric Synthesis of α-Alkylmandelic Acids Utilizing Highly Diastereoselective Alkylation of 5-Aryl-2-(1-naphthyl)-1,3-dioxolan-4-ones

Tomonori Misaki, Satoko Ureshino, Ryohei Nagase, Yumiko Oguni, and Yoo Tanabe*

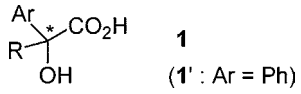
Department of Chemistry, School of Science and Technology, Kwansei Gakuin University, 2-1 Gakuen, Sanda, Hyogo 669-1337, Japan

Abstract:

A practical method for the synthesis of optically pure α-alkylmandelic acids 1 is described. The present improved robust method involved two reactions: a mild, convenient, stereoselective preparation of chiral *cis*-5-aryl-2-(1-naphthyl)-1,3-dioxolan-4-ones, 9a−c, and highly diastereoselective alkylation of 9a−c, followed by the hydrolysis.

Introduction

Optically active α-alkylmandelic acids **1**, including atrolactic acids (**1**, R = CH_3),[1] are recognized as an important chemical class of chiral auxiliaries,[1k,2] chiral catalysts,[3] optical resolution reagents (e.g., the Mosher's reagent),[4] and pharmaceuticals (e.g., a muscarinic receptor antagonist).[5]

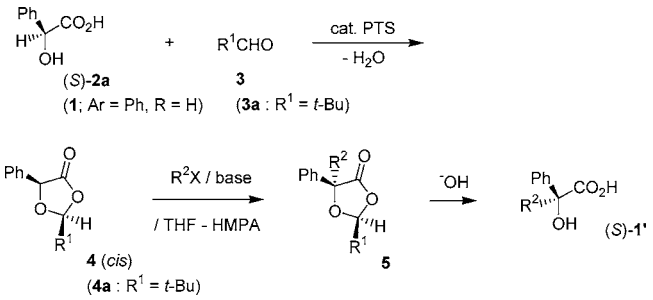


1

(**1**' : Ar = Ph)

Seebach and co-workers exploited the original asymmetric synthesis of these compounds **1′** utilizing diastereoselective alkylation of chiral 2-substituted (representatively, R^1 = 2-*t*-Bu) *cis*-5-phenyl-1,3-dioxolan-4-ones, **4**, derived from (*S*)-mandelic acid (*S*)-**2a** and aldehydes **3**, followed by deacetalization (hydrolysis) to give (*S*)-α-alkylmandelic acids (*S*)-**1′** (Scheme 1).[6] The Fráter group independently reported the same method and applied it to the synthesis of (*S*)-atrolactic acid [(*S*)-**1′** (R^2 = CH_3].[7]

Scheme 1



There are other approaches utilizing diastereoselective nucleophilic addition to (−)-phenylmenthyl α-oxophenylacetate[8] and catalytic asymmetric addition of R_2Zn or CH_3-MgI to methyl α-oxophenylacetate.[5d,9]

Despite the increasing synthetic value, a more practical synthetic method is needed, because some drawbacks remain: (i) besides the Seebach and Fráter methods,[6,7] all of the other reported methods require expensive and/or complex chiral auxiliaries and catalysts; (ii) the syntheses of atrolactic acid (**1′**, R = CH_3), an important analogue, resulted in moderate stereoselectivity (76−86% ee), except for Shibasaki's method (92% ee);[9b] and (iii) the preparation of precursor **4** involved a somewhat tedious procedure (vide supra). Our ongoing study of the asymmetric version of Ti-crossed Claisen condensation[10] necessitated the preparation of (*S*)-atrolactic acids [(*S*)-**1′**; R = CH_3] with high optical purity. Herein, we describe an improved procedure for the synthesis of chiral α-alkylmandelic acids (**1**; R = CH_3, others) utilizing highly diastereoselective alkylation of chiral 5-aryl-2-(1-naphthyl)-1,3-dioxolan-4-ones, **9a**−**c**. These in-

* To whom correspondence should be addressed. E-mail: tanabe@kwansei.ac.jp.

(1) (a) McKenzie, A.; Clough, G. W. *J. Chem. Soc.* **1910**, 1016. (b) Smith, L. *J. Prakt. Chem.* **1911**, *115*, 731. (c) Inch, T. D.; Ley, R. V.; Rich, P. *J. Chem. Soc. C* **1968**, 1693. (d) Meyers, A. I.; Slade, J. *Synth. Commun.* **1976**, *6*, 601. (e) Boireau, G.; Abenhaim, D.; Deberly, A.; Sabourault, B. *Tetrahedron Lett.* **1982**, *23*, 1259. (f) Lynch, J. E.; Eliel, E. L. *J. Am. Chem. Soc.* **1984**, *106*, 2943. (g) Solladie-Cavallo, A.; Suffert, J. *Tetrahedron Lett.* **1984**, *25*, 1897. (h) He, X. C.; Eliel, E. L. *Tetrahedron* **1987**, *43*, 4979. (i) Boireau, G.; Deberly, A.; Abenhaim, D. *Tetrahedron* **1989**, *45*, 5837. (j) Pansare, S. V.; Ravi, R. G. *Tetrahedron* **1998**, *54*, 14549. (k) Crane, S. N.; Corey, E. J. *Org. Lett.* **2001**, *3*, 1395. (l) Koshiishi, E.; Hattori, T.; Ichihara, N.; Miyano, S. *J. Chem. Soc., Perkin Trans. 1* **2002**, 377. (m) Prisinzano, T.; Hsin, L.-W.; Folk, J. E.; Flippen-Anderson, J. L.; George, C.; Jacobson, A. E.; Rice, K. C. *Tetrahedron: Asymmetry* **2003**, *14*, 3285.

(2) Tripathy, R.; Carroll, P. J.; Thornton, E. R. *J. Am. Chem. Soc.* **1991**, *113*, 7630.

(3) Buck, R. T.; Coe, D. M.; Drysdale, M. J.; Ferris, L.; Haigh, D.; Moody, C. J.; Pearson, N. D.; Sanghera, J. B. *Tetrahedron: Asymmetry* **2003**, *14*, 791.

(4) (a) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543. (b) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512.

(5) (a) Grover, P. T.; Bhongle, N. N.; Wald, S. A.; Senanayake, C. H. *J. Org. Chem.* **2000**, *65*, 6283. (b) Mase, T.; Houpis, I. N.; Akao, A.; Dorziotis, I.; Emerson, K.; Hoang, T.; Iida, T.; Itoh, T.; Kamei, K.; Kato, S.; Kato, Y.; Kawasaki, M.; Lang, F.; Lee, J.; Lynch, J.; Maligres, P.; Molina, A.; Nemoto, T.; Okada, S.; Reamer, R.; Song, J. Z.; Tschaen, D.; Wada, T.; Zewge, D.; Volante, R. P.; Reider, P. J.; Tomimoto, K. *J. Org. Chem.* **2001**, *66*, 6775. (c) Gupta, P.; Fernandes, R. A.; Kumar, P. *Tetrahedron Lett.* **2003**, *44*, 4231. (d) Masumoto, S.; Suzuki, M.; Kanai, M.; Shibasaki, M. *Tetrahedron* **2004**, *60*, 10497.

(6) (a) Seebach, D.; Naef, R. *Helv. Chem. Acta* **1981**, *64*, 2704. (b) Seebach, D.; Sting, A. R.; Hoffmann, M. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2708.

(7) Fráter, G.; Müller, U.; Günther, W. *Tetrahedron Lett.* **1981**, *22*, 4221.

(8) (a) Whitesell, J. K.; Deyo, D.; Bhattacharya, A. *J. Chem. Soc., Chem. Commun.* **1983**, 802. (b) Esser, P.; Buschmann, H.; Meyer-Stork, M.; Scharf, H.-D. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 1190. (c) Wipf, P.; Stephenson, C. R. J. *Org. Lett.* **2003**, *5*, 2449.

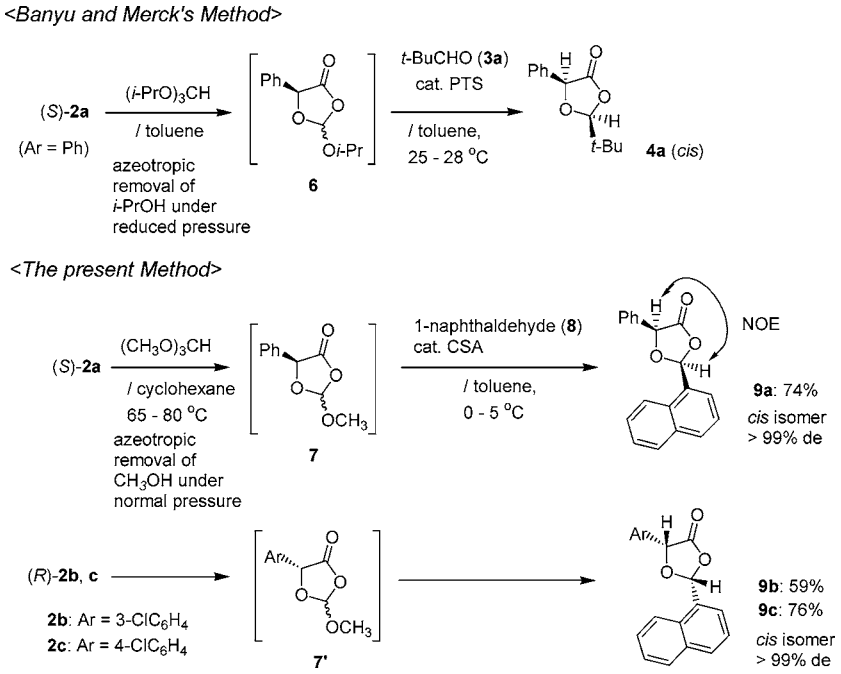
(9) (a) DiMauro, E. F.; Kozlowski, M. C. *J. Am. Chem. Soc.* **2002**, *124*, 12668. (b) Funabashi, K.; Jachmann, M.; Kanai, M.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2003**, *42*, 5489.

(10) (a) Tanabe, Y. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 1917. (b) Misaki, T.; Nagase, R.; Matsumoto, K.; Tanabe, Y. *J. Am. Chem. Soc.* **2005**, *127*, 2854 and references therein.

Published on Web 03/21/2006

10.1021/op050263j CCC: $33.50

Scheme 2



termediates were prepared from readily available and inexpensive materials, chiral mandelic acids **2a**−**c** and 1-naphthaldehyde, **8**, under mild and practical reaction conditions.

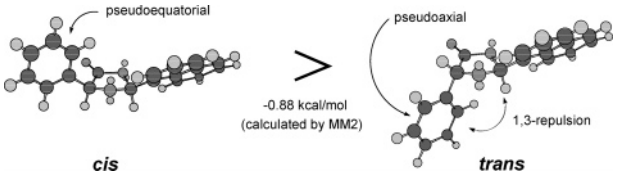
Results and Discussion

The method utilizing the chiral template, 2,5-disubstituted 1,3-dioxolan-4-ones, **4**, includes two highly diastereoselective reactions, i.e., a cis selective cyclocondensation between optically active mandelic acids **2** and specific aldehydes **3**, followed by a trans selective alkylation of **4**. Previous studies suggested that the use of pivalaldehyde (**3a**; R^1 = *t*-Bu) afforded the best result among other carbonyl compounds, such as isobutyraldehyde,[7] benzaldehyde,[11] and acetophenone.[11]

There are a few problems in the reaction conditions of the original stereoselective condensation between **2** and **3a**, because of the low reactivity of **3a** and the purification procedure. Banyu and Merck's groups reported an improved practical method, using $(i\text{-PrO})_3$CH/PTS catalyst as an effective formal dehydrating agent for the preparation of 2-(*tert*-butyl)-5-phenyl-1,3-dioxolane-4-one (**4a**; R^1 = *t*-Bu, 92%) (Scheme 2).[5b] They utilized the chiral synthon **4a** for a stereoselective Michael addition to cyclopentenone and performed an efficient practical synthesis of a muscarinic receptor antagonist. A related method using a $(i\text{-PrO})_3$CH/Rh(III) catalyst was also reported.[12] These backgrounds prompted us to investigate a more convenient and cost-effective method of utilizing novel 5-aryl-2-(1-naphthyl)-1,3-dioxolane-4-ones, **9a**−**c**, from mandelic acids **2a** (2*S*), **2b** (2*R*, commercially available), **2c** (prepared by classical resolution),[13] leading to chiral α-alkylmandelic acids, (*S*)-**1′**, (*R*)-**19**−**22**.

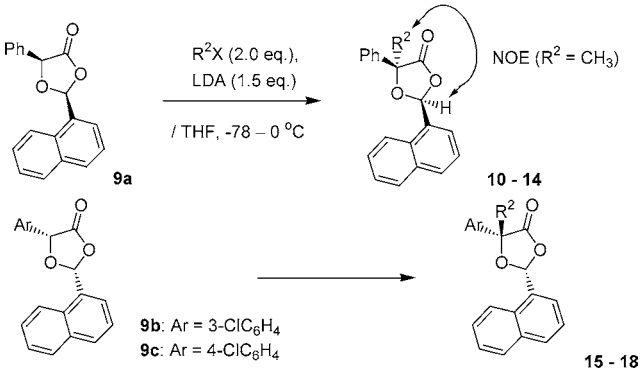
As shown in Scheme 2, the present method has several advantages concerning the first step of *cis*-1,3-dioxolan-4-ones formation, such as (i) both $(CH_3O)_3$CH and 1-naphthaldehyde, **8**, are more inexpensive than $(i\text{-PrO})_3$CH and pivalaldehyde, **3a**; (ii) due to the higher reactivity of $(CH_3O)_3$CH, relatively unstable intermediate **7** (or **7′**) was smoothly formed at lower temperature and shorter reaction periods than those of **6**;[14] (iii) the desired *cis*-1,3-dioxolan-4-ones, **9a**−**c**, were formed more smoothly than **4a**,[15] due to the higher reactivity;[16] the reaction between **7** (or **7′**) and **3a** resulted in 10−30% yield under identical conditions; and (iv) the crude chiral products **9a**−**c** (>90% de) were easily purified by one recrystallization (>99% de). The relative *cis* configuration was determined using **9a** by NOE measurement

(11) Farines, M.; Soulier, J. *Bull. Chem. Soc. Fr.* **1970**, 332.
(12) Ott, J.; Tombo, G. M. R.; Schmid, B.; Venanzi, L. M.; Wang, G.; Ward, T. R. *Tetrahedron Lett.* **1989**, *30*, 6151.
(13) Nieuwenhuijzen, J. W.; Grimbergen, R. F. P.; Koopman, C.; Kellogg, R. M.; Vries, T. R.; Pouwer, K.; van Echten, E.; Kaptein, B.; Hulshof, L. A.; Broxterman, Q. B. *Angew. Chem., Int. Ed.* **2002**, *41*, 4281.
(14) Intermediates **6**, **7**, and **7′** were not be isolable, due to the thermal instability. Private communication from the Banyu group: A careful technique of azeotropic removal of *i*-PrOH under reduced pressure at low temperature was required to generate intermediate **6**.
(15) Because a conformational effect, such as 2-(1-naphthyl)- and 5-aryl-substituents of **9**, would occupy a pseudoequatorial position, *cis*-acetal formation should be thermodynamically favoured. (a) Clayden, J.; Greeves, N.; Warren, S.; Wothers, P. *Organic Chemistry*; Oxford: New York, 2001; p 855. (b) A computer-assisted conformation analysis, exemplified by **9a**, supports this speculation [MM2 force field, ChemBats3D 5.0 Windows, CambridgeSoft Corporation: Cambridge, Massachusetts]. (c) A relevant discussion in the case of a related isoster, 2,5-disubstituted 4-thazolidin-4-ones; Tanabe, Y.; Yamamoto, H.; Murakami, M.; Yanagi, K.; Kubota, Y.; Okumura, H.; Sanemitsu, Y.; Suzukamo, G. *J. Chem. Soc., Perkin Trans. 1* **1995**, 935.



(16) Probably because intermediary 1-naphthylmethylinum cation was generated more smoothly than *tert*-butylmethylinium cation, 1-naphthaldehyde underwent rapid and safe acetal formation to give **9**.

Table 1. **Diastereoselective trans alkylation of 9a−c**



entry	substrate	R^2X	product	yield (%)[a]	de (%)[b]
1	**9a** (*S*)	CH_3I	**10** (2*S*,5*S*)	79	92
2	**9a**	$PhCH_2Br$	**11** (2*S*,5*S*)	76	>95
3	**9a**	$CH_2{=}CHCH_2Br$	**12** (2*S*,5*S*)	72	>95
4	**9a**	$CH_3(CH_2)_3I$	**13** (2*S*,5*S*)	58	>95
5	**9a**	$EtO_2C(CH_2)_2Br$	**14** (2*S*,5*S*)	57	>95
6	**9b** (*R*)	CH_3I	**15** (2*R*,5*R*)	64[c]	93[d]
7	**9b**	$PhCH_2Br$	**16** (2*R*,5*R*)	34[c]	98[d]
8	**9c** (*R*)	CH_3I	**17** (2*R*,5*R*)	54	92
9	**9c**	$PhCH_2Br$	**18** (2*R*,5*R*)	66	90

[a] Isolated. [b] Determined by ^1H NMR of the crude product. [c] Yield based on the corresponding α-alkylmandelic acids **20**, **21** (See Experimental Section). [d] Determined by HPLC analysis (ee) of **20** and **21**.

of ^1H NMR. Because of the sensitive conditions of the present reaction, CSA was used as the catalyst, instead of hygroscopic and stronger acidic PTS; the use of PTS resulted in more rapid reaction, however, with moderate cis selectivity (ca. cis:trans = 8:2).

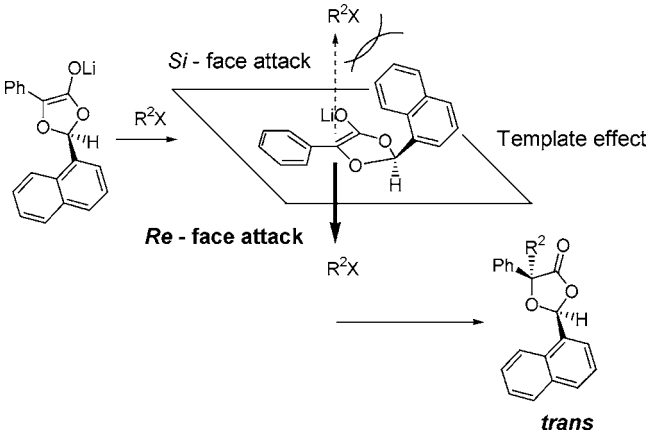
The next alkylation step using **9a**−**c** proceeded with high trans diastereoselectivity to give the desired chiral products **10**−**18**, and Table 1 summarizes these successful results. The salient features are as follows: (i) the selectivity using **9a**−**c** was no less than that using **4a**, (ii) the reaction leading to (*S*)-atrolactic acid [(*S*)-**1a**] had higher efficiency (entry 1) (**4a**; 86% ee, **9a**; 92% ee),[7] (iii) stereochemistry of product **10** was unambiguously determined by NOE measurement of ^1H NMR, (iv) four other alkyl halides underwent the desired reaction with **9a** (entries 2−5), (v) other new analogues **9b** and **9c** were also obtained (entries 6−9), and (vi) note that toxic and hazardous HMPA cosolvent was unnecessary and was eliminated during the alkylation step in contrast to the reported methods.[6,7]

The proposed mechanism of trans diastereoselective alkylation is depicted in Scheme 3. Due to the template effect, steric repulsion between the 1-naphthyl group and R^2X (alkyl halides) caused enhancement of *re*-face attack over the *si*-face attack, thus leading to trans products.

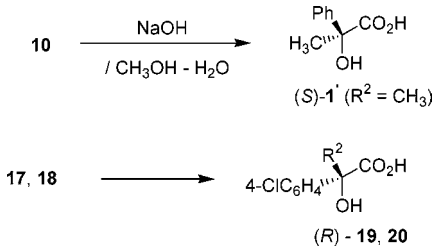
Finally, several optically active α-alkylmandelic acids, (*S*)-**1′** and (*R*)-**19**−**22**, were obtained by the conventional deacetalization (hydrolysis)[7] in good yield without loss of enantioselectivity (Scheme 4).

In conclusion, we developed a practical, improved method for the synthesis of chiral α-alkylmandelic acids **1**, including atrolactic acids (**1a**; $R^4 = CH_3$), utilizing an accessible novel 5-aryl-2-(1-naphthyl)-1,3-dioxolane-4-one precursors, **9a**−**c**. The present robust method will provide a new and easy access to chiral synthons and ligands for process research.

Scheme 3



Scheme 4



Experimental Section

General. Melting points were determined on a hot stage microscope apparatus (Yanagimoto) and were uncorrected. NMR spectra were recorded on a JEOL DELTA 300 spectrometer, operating at 300 MHz for ^1H NMR and 75 MHz for ^{13}C NMR. Chemical shifts (δ ppm) in $CDCl_3$ were reported downfield from TMS (= 0) for ^1H NMR. For ^{13}C NMR, chemical shifts were reported in the scale relative to $CDCl_3$ (77.00 ppm) as an internal reference. IR Spectra were recorded on a JASCO FT/IR-5300 spectrophotometer. The enantiomeric excess (ee) was determined by HPLC analysis. HPLC data were obtained on a SHIMADZU HPLC system (consisting of the following: SLC-10A, DGU-12A, LC-10AD, SIL-10A, CTO-10A, and detector SPD-10AV, measured at 254 nm) using DAICEL Chiralpak AD-H column (0.46 cm × 25 cm) at 35 °C. Optical rotations were measured on a JASCO DIP-370 (Δ 589 nm). Mass spectra were measured on a JEOL JMS-T100LC spectrometer.

Typical Procedure for the Preparation of (2*S*,5*S*)-2-(1-Naphthyl)-5-phenyl-1,3-dioxolan-4-one (9a). A solution of (*S*)-mandelic acid (**2a**; 15.2 g, 100 mmol) and $(CH_3O)_3$-CH (15.9 g, 150 mmol) in cyclohexane (100 mL) was stirred at 65−80 °C using Dean−Stark apparatus with continual azeotropic removal of CH_3OH−cyclohexane (∼45 mL) for ∼1 h under an Ar atmosphere. After cooling to room temperature, the remaining cyclohexane and $(CH_3O)_3CH$ were removed under reduced pressure 35−40 °C using a rotary evaporator and vacuum pump. Toluene (50 mL) was added to the resultant residue (not viscous oil), which was cooled to 0−5 °C. After addition of (+)-10-camphorsulfonic

acid (697 mg, 3.0 mmol), to the mixture was added dropwise for ca. 20 min 1-naphthaldehyde (**8**; 17.2 g, 110 mmol) in toluene (5 mL). After stirring at the same temperature for 1 h, the mixture was seeded with material (>∼90% de) from a small-scale preparation. After ∼30 min, white precipitates of the desired product **9a** gradually appeared and increased. The slurry was stirred at that temperature for 3 h, and it was quenched with saturated $NaHCO_3$ aqueous solution, which was extracted twice with AcOEt. The combined organic phase was washed with water and brine, dried (Na_2SO_4), and concentrated. The obtained crude product (92% de based on ^1H NMR measurement) was collected, using a glass filter, washing with 100 mL of hexanes−Et_2O (2:1). The resultant crude solid was purified by recrystallization from AcOEt (ca. 30 mL) to give **9a** (21.4 g, 74%, >99% de).

Colorless crystals; mp 132−133 °C; $[\alpha]^{25}_D$ +65.5 (*c* 0.99, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 5.54 (s, 1H), 7.25 (s, 1H), 7.35−7.45 (m, 3H), 7.45−7.62 (m, 5H), 7.88−7.99 (m, 3H), 8.09−8.16 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 77.13, 101.30, 123.08, 124.11, 125.05, 126.24, 127.06, 127.10, 128.80, 128.86, 129.32, 129.68, 130.46, 131.00, 133.35, 133.64, 171.29; IR (KBr) 1786, 1244, 1211, 1159, 941, 783 cm^{-1}; HRMS (ESI) calcd for $C_{19}H_{14}O_3$ (M + Na^+) 313.0841, found 313.0843.

(2*R*,5*R*)-5-(3-Chlorophenyl)-2-(1-naphthyl)-1,3-dioxolan-4-one (9b): colorless crystals; mp 105−110 °C; $[\alpha]^{25}_D$ −79.9 (*c* 1.02, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 5.49 (s, 1H), 7.22 (s, 1H), 7.26−7.41 (m, 3H); 7.45−7.62 (m, 4H), 7.82−8.00 (m, 3H), 8.05−8.14 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 76.18, 101.49, 122.97, 124.09, 124.97, 125.03, 126.29, 126.98, 127.10, 128.89, 129.35, 129.41, 130.04, 130.37, 131.13, 133.64, 134.73, 135.13, 170.62; IR (KBr) 3063, 2949, 1788, 1412, 1206 cm^{-1}; HRMS (ESI) calcd for $C_{19}H_{13}ClO_3$ (M + Na^+) 347.0451, found 347.0455.

(2*R*,5*R*)-5-(4-Chlorophenyl)-2-(1-naphthyl)-1,3-dioxolan-4-one (9c): colorless crystals; mp 105−109 °C; $[\alpha]^{25}_D$ −87.1 (*c* 1.61, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 5.50 (s, 1H), 7.23 (s, 1H), 7.32−7.46 (m, 4H); 7.48−7.64 (m, 3H), 7.80−8.01 (m, 3H), 8.06−8.15 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 76.31, 101.48, 122.99, 124.06, 125.031, 126.29, 127.10, 128.25, 128.90, 129.91, 129.22, 129.43, 130.37, 131.11, 133.64, 135.30, 70.90; IR (KBr) 3063, 2946, 1788, 1491, 1208, 941 cm^{-1}; Anal. Calcd for $C_{19}H_{13}ClO_3$: C, 70.3; H, 4.0, found: C, 70.0; H, 3.8.

Typical Procedure for the Trans Selective Alkylation of 9a with CH_3I. BuLi (1.58 M in hexane, 19.7 mL, 31.1 mmol) was added to a stirred solution of $^iPr_2NH$ (3.41 g, 33.7 mmol) in THF (15 mL) at −10 °C under an Ar atmosphere, and the mixture was stirred at the same temperature for 30 min. After cooling the mixture to −78 °C, a solution of **9a** (7.53 g, 26.0 mmol) in THF (25 mL) was slowly added to the mixture, which was stirred at the same temperature for 30 min. A solution of CH_3I (7.37 g, 51.9 mmol) in THF (5 mL) was slowly added to the mixture, which was stirred at the same temperature for 5 min, and then warmed to 0−5 °C during about 2.5 h. The mixture was quenched with water (200 mL), which was extracted twice with ether. The combined organic phase was washed with water and brine, dried (Na_2SO_4), and concentrated. The obtained crude oil (92% de based on ^1H NMR measurement) was purified by SiO_2-column chromatography (hexane−AcOEt = 30:1 to 20:1) to give (2*S*,5*S*)-5-methyl-2-(1-naphthyl)-5-phenyl-1,3-dioxolan-4-one (**10**; 6.20 g, 79%, 92% de).

Colorless liquid; $[\alpha]^{25}_D$ +64.4 (*c* 1.21, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 1.97 (s, 1H), 7.22−7.35 (m, 4H), 7.44 (dd, 1H, *J* = 7.2, 8.3 Hz), 7.51−7.62 (m, 4H), 7.70−7.77 (m, 1H), 7.85−7.95 (m, 2H), 8.09−8.20 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.69, 79.98, 99.83, 123.21, 124.00, 124.96, 124.99, 126.16, 126.92, 128.26, 128.36, 128.82, 130.25, 130.42, 130.69, 133.64, 138.99, 173.73; IR (KBr) 3063, 2978, 2932, 1795, 1217, 1132, 966 cm^{-1}; HRMS (ESI) calcd for $C_{20}H_{16}O_3$ (M + Na^+) 327.0997, found 327.1001.

(2*S*,5*S*)-5-Benzyl-2-(1-naphthyl)-5-phenyl-1,3-dioxolan-4-one (11): colorless crystals; mp 101−104 °C; $[\alpha]^{25}_D$ +15.5 (*c* 1.02, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 3.33 (d, 1H, *J* = 13.8 Hz), 3.68 (d, 1H, *J* = 13.8 Hz), 6.34 (s, 1H), 7.25−7.89 (m, 17H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 45.91, 83.79, 101.04, 123.08, 123.43, 124.94, 124.99, 126.05, 126.79, 127.75, 129.32, 128.21, 128.34, 128.72, 130.25, 130.44, 130.54, 130.71, 133.52, 134,57, 138.72, 173.12; IR (KBr) 3061, 3030, 1804, 1784, 1182 cm^{-1}; HRMS (ESI) calcd for $C_{26}H_{20}O_3$ (M + Na^+) 403.1310, found 403.1301.

(2*S*,5*S*)-2-(1-Naphthyl)-5-phenyl-5-(2-propenyl)-1,3-dioxolan-4-one (12): colorless crystals; mp 96−99 °C; $[\alpha]^{25}_D$ +63.7 (*c* 1.33, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ2.91 (dd, 1H, *J* = 7.2, 14.5 Hz), 3.68 (dd, 1H, *J* = 6.8, 14.4 Hz), 5.24−5.40 (m, 2H), 5.85−6.04 (m, 1H), 7.17−7.47 (m, 4H), 7.47−7.68 (m, 5H), 7.84−7.94 (m, 2H), 8.07−8.17 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 43.33, 82.53, 100.90, 121.06, 121.18, 123.24, 123.66, 124.92, 125.03, 126.12, 126.91, 128.13, 128.23, 128.80, 130.33, 130.54, 130.79, 133.62, 137.88, 172.89; IR (KBr) 3067, 2913, 1346, 1206, 1105 cm^{-1}; HRMS (ESI) calcd for $C_{22}H_{18}O_3$ (M + Na^+) 353.1154, found 353.1150.

(2*S*,5*S*)-5-Butyl-2-(1-naphthyl)-5-phenyl-1,3-dioxolan-4-one (13): colorless liquid; $[\alpha]^{25}_D$ +64.2 (*c* 1.00, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 0.82−0.99 (m, 3H), 1.17−1.67 (m, 4H), 2.09−2.38 (m, 2H); 7.19−7.27 (m, 3H), 7.32 (s, 1H), 7.37−7.75 (m, 6H), 7.85−8.05 (m, 2H), 8.13−08.19 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.90, 22.60, 25.85, 38.16, 82.68, 100.56, 123.27, 123.77, 124.92, 125.01, 126.12, 126.89, 127.92, 128.15, 128.82, 130.37, 130.52, 130.90, 133.64, 138.05, 173.54; IR (KBr) 3063, 2959, 2870, 1794, 1196 cm^{-1}; HRMS (ESI) calcd for $C_{23}H_{22}O_3$ (M + Na^+) 369.1467, found 369.1468.

(2*S*,5*S*)-5-(2-Ethoxycarbonylethyl)-2-(1-naphthyl)-5-phenyl-1,3-dioxolan-4-one (14): colorless liquid; $[\alpha]^{25}_D$ +69.3 (*c* 1.23, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 1.23 (t, 3H), 2.29−2.58 (m, 3H), 2.66−2.81 (m, 1H), 4.13 (q, 2H, *J* = 7.2 Hz), 7.22−7.29 (m, 3H), 7.33 (s, 1H), 7.38−7.68 (m, 6H), 7.87−7.94 (m, 2H), 8.11−8.17 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.15, 28.80, 32.45, 60.73, 81.61, 100.42, 132.26, 123.94, 124.90, 125.13, 126.18, 126.95, 128.30, 128.34, 128.82, 130.37, 130.43, 130.69, 133.62, 136.68, 172.55, 172.82; IR (KBr) 2982, 2932, 1796, 1732,

1198 cm^{-1}; HRMS (ESI) calcd for $C_{24}H_{22}O_5$ ($M + Na^+$) 413.1365, found 413.1361.

(2*R*,5*R*)-5-(3-Chlorophenyl)-5-methyl-2-(1-naphthyl)-1,3-dioxolan-4-one (15). Because of the instability of **15** for the SiO_2 and alumina column chromatographic purifications, the crude product was converted to (2*R*)-2-(3-chlorophenyl)-2-hydroxypropanoic acid (**20**): colorless crystals; mp 104 − 105 °C; $[\alpha]^{25}_D$ −57.9 (*c* 0.81, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 1.81 (s, 3H), 7.25−7.33 (m, 2H), 7.43−7.51 (m, 1H); 7.57−7.61 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.83, 75.31, 123.52, 125.70, 128.36, 129.72, 134.52, 143.69, 179.97; IR (KBr) 3416, 3287, 2994, 1718, 1260, 1150 cm^{-1}; HRMS (ESI) calcd for $C_9H_9ClO_3$ ($M - H^+$) 199.0162, found 199.0165. HPLC analysis [flow rate: 0.80 mL/min, solvent: hexane/2-propanol/TFA = 90/10/1, t_R(racemic) = 12.67 and 15.17 min, t_R(**20**) = 12.68 min (minor) and 15.17 min (major)] 93% ee.

(2*R*,5*R*)-5-Benzyl-5-(3-chlorophenyl)-2-(1-naphthyl)-1,3-dioxolan-4-one (16). Due to the same reason, the crude product was converted to (2*R*)-2-(3-chlorophenyl)-2-hydroxy-3-phenylpropanoic acid (**21**): colorless crystals; mp 148−150 °C; $[\alpha]^{25}_D$ −28.8 (*c* 0.89, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 3.18 (d, 1H, *J* = 13.76), 3.60. (d, 1H, *J* = 13.76), 4.75.-6.50 (brs, 1H), 7.17−7.36 (m, 7H); 7.56−7.63 (m, 1H), 7.69−7.73 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 45.92, 78.24, 124.00, 126.14, 127.38, 128.38, 129.64, 130.42, 134.46, 134.52, 142.49, 178.06; IR (KBr) 3443, 2976, 1725, 1188, 1107 cm^{-1}; HRMS (ESI) calcd for $C_{15}H_{13}ClO_3$ ($M - H^+$) 275.0475, found 275.0472. HPLC analysis [flow rate: 0.80 mL/min, solvent: hexane/2-propanol/TFA = 90/10/1, t_R(racemic) = 14.17 and 18.42 min, t_R(**21**) = 14.11 min (minor) and 18.33 min (major)]; 98% ee.

(2*R*,5*R*)-5-(4-Chlorophenyl)-5-methyl-2-(1-naphthyl)-1,3-dioxolan-4-one (17): colorless crystals; mp 66−70 °C; $[\alpha]^{25}_D$ −98.0 (*c* 0.77, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 1.93 (s, 3H), 7.21−7.32 (m, 3H), 7.40−7.62 (m, 5H), 7.65−7.72 (m, 1H), 7.85−7.96 (m, 2H), 8.07−8.16 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.98, 79.52, 99.98, 123.11, 123.90, 124.9, 126.22, 126.41, 126.98, 128.51, 128.88, 130.08, 130.33, 130.80, 133.64, 134.32, 137.56, 173.37; IR (KBr) 3065, 2982, 1798, 1215, 1132, 787 cm^{-1}; Anal. Calcd for $C_{20}H_{15}ClO_3$: C, 70.9; H, 4.5, found: C, 70.2; H, 4.3.

(2*R*,5*R*)-5-Benzyl-5-(4-chlorophenyl)-2-(1-naphthyl)-1,3-dioxolan-4-one (18): colorless crystals; mp 105−109 °C; $[\alpha]^{25}_D$ −7.58 (*c* 0.59, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 3.29 (d, 1H, *J* = 13.8 Hz), 3.65 (d, 1H, *J* = 13.8 Hz), 6.39 (s, 1H), 7.23−7.29 (m, 3H), 7.32−7.49 (m, 5H), 7.52−7.59 (m, 5H), 7.81−7.91 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 45.81, 83.29, 101.11, 122.94, 123.33, 124.90, 126.10, 126.47, 126.85, 127.82, 128.47, 128.73, 130.15, 130.50, 130.56, 133.52, 134.15, 134.27, 137.14, 172.76; IR (KBr) 3065, 1792, 1491, 1250, 1192, 1094 cm^{-1}; HRMS (ESI) calcd for $C_{26}H_{19}ClO_3$ ($M + Na^+$) 437.0920, found 437.0914,

(2*S*)-2-Hydroxy-2-phenylpropanoic Acid, (*S*)-Atrolactic Acid [(*S*)-1′; R = CH_3]. In a manner similar to the preparation of **10**, the use of **9a** (20.4 g, 70.2 mmol) and CH_3I (19.9 g, 140.3 mmol) gave the crude oil (92% de based on ^1H NMR measurement), which was dissolved in CH_3OH (50 mL), and 2.5 M NaOH aqueous solution (50 mL) was added to the mixture at 0−5 °C. After stirring at room temperature for 1 h, the mixture was extracted twice with ether. The aqueous layer was adjusted to pH 2−3 using 6 M HCl aqueous solution, which was re-extracted twice with AcOEt. The combined organic phase was washed with water and brine, dried (Na_2SO_4), and concentrated. The obtained crude crystals were washed with cooled toluene (ca. 50 mL) over a glass filter and purified by recrystallization twice from toluene to give the product (6.29 g, 54%).

Colorless crystals; mp 112−114 °C; $[\alpha]^{23}_D$ +36.0 (*c* 0.99, C_2H_5OH) (lit.[1a] +37.7, C_2H_5OH); ^1H NMR (300 MHz, $CDCl_3$) δ 1.83 (s, 3H), 7.27−7.40 (m, 3H), 7.52−7.61 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.58, 75.70, 125.15, 128.17, 128.46, 141.71, 180.54; IR (KBr) 3420, 2953, 1713, 1260, 1140, 891 cm^{-1}. HPLC analysis [flow rate: 0.80 mL/min, solvent: hexane/2-propanol/TFA = 90/10/1, t_R(racemic) = 14.12 and 17.80 min, t_R(**13**) = 14.08 min] > 99% ee.

(2*R*)-2-(4-Chlorophenyl)-2-hydroxypropanoic acid (19): colorless crystals; mp 168−169 °C; $[\alpha]^{26}_D$ −38.9 (*c* 1.01, C_2H_5OH).

(2*R*)-2-(4-Chlorophenyl)-2-hydroxy-3-phenylpropanoic acid (20): colorless crystals; mp 206−209 °C; $[\alpha]^{25}_D$ +12.0 (*c* 1.24, C_2H_5OH).

Acknowledgment

This research was partially supported by Grant-in-Aids for Scientific Research on Priority Areas (A) "17035087" and Exploratory Research "17655045" from the Ministry of Education, Culture, Sports, Science and Technology (MEXT).

Received for review December 28, 2005.

OP050263J