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Diastereoselective Synthesis of the Acid Part of a New Muscarinic M_3 Receptor Antagonist

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Abstract—Diastereoselective synthesis of (2*R*)-2-[(1*R*)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetic acid **1**, an important component of a novel muscarinic M_3 receptor antagonist **3**, was achieved via Michael addition of an enolate of chiral dioxolane **4** to (−)-dicyclopentadiene **9** in 90% de as a key step. The desired Michael adduct **10**, which was easily isolated by recrystallization of a mixture of diastereomers, was submitted to retrograde Diels–Alder reaction. Subsequent hydrogenation of the resultant enone **12** gave the key intermediate **5** in 91% chemical yield from **10**.

Introduction

Compound **3** is a long-acting, orally active muscarinic receptor antagonist with 190-fold selectivity for M_3 over M_2 receptors.[1] This compound is now being developed for the treatment of urinary tract disorders such as urinary incontinence (UI) and respiratory disorders such as chronic obstructive pulmonary disease (COPD).

The muscarinic M_3 receptor antagonist **3** consists of a unique chiral difluorinated cyclopentylphenylacetic acid fragment **1** and an 4-amino-1-(aminopyridylmethyl)-piperidine moiety **2** connected through an amide bond (Fig. 1). The original synthesis of this acid **1** included Michael addition of an enolate of **4**[2] to 2-cyclopenten-1-one and subsequent chromatographic separation of the diasteromeric mixture of Michael adducts (**5**:**6**=1.2:1) to obtain the key intermediate **5** (Scheme 1).[3,4] We considered it desirable to produce **5** diastereoselectively to streamline the synthesis of **1**. In this paper, we describe a synthesis of **1** involving a diastereoselective preparation of **5**.

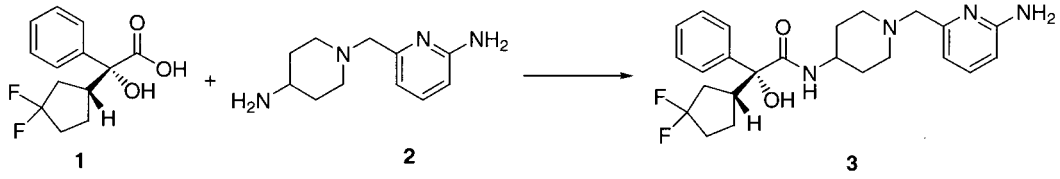
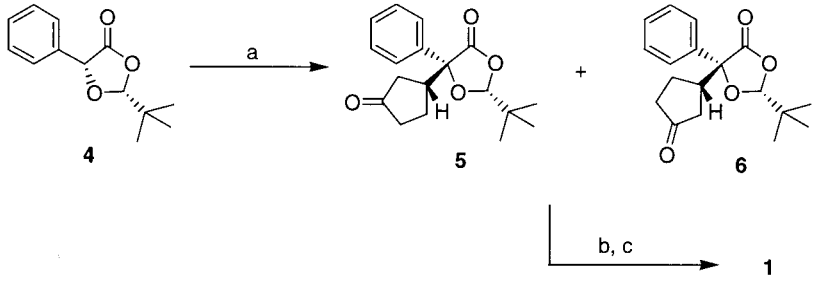


Figure 1.



Scheme 1. Conditions: (a) LDA, 2-cyclopenten-1-one, THF, −78°C. (b) DAST, $CHCl_3$, 70°C. (c) NaOH, MeOH, rt.

Keywords: muscarinic receptor; antagonist; Michael addition; enolate.

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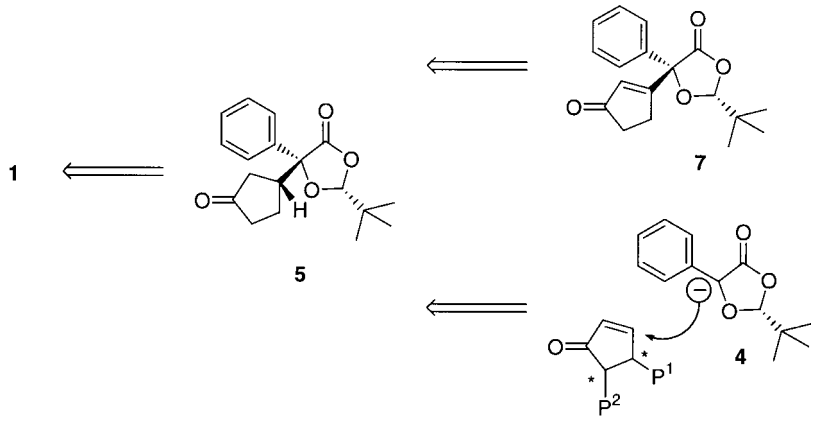
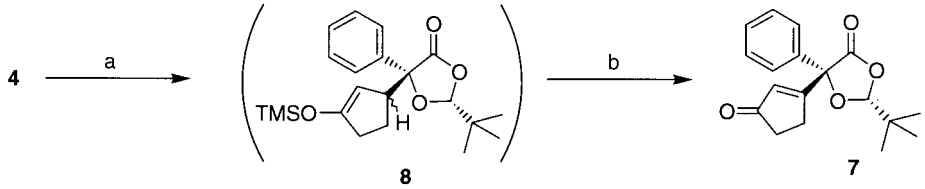
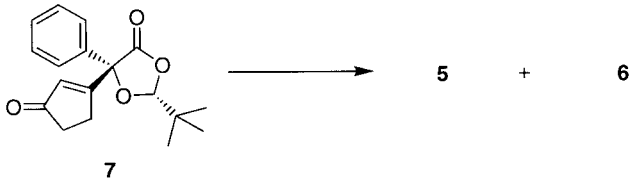


Figure 2.



Scheme 2. Conditions: (a) LDA, 2-cyclopenten-1-one, THF, −70°C, then TMSCl. (b) $Pd(OAc)_2$, *p*-benzoquinone, CH_3CN, rt.

Table 1. 1,4-Reduction of **7**



Run	Condition	Ratio of **5** and **6**[a]	Yield (%)
1	H_2, Pd–C, EtOAc	1:1.2	99
2	H_2, Pd–C, EtOH	1:1.4	97
3	H_2, Pd–C, THF	1:1.3	89
4	H_2, Rh–Al_2O_3, EtOAc	1.2:1	88
5	CuI, DIBAL, THF–HMPA	1:1.2	76
6	$[(Ph_3P)CuH]_6$, $PhSiH_3$, benzene	1:1.2	73
7	Ph_2SiH_2, $Pd(PPh_3)_4$, $ZnCl_2$, $CHCl_3$	1.1:1	72

[a] Determined by ^1H NMR of the crude reaction mixture.

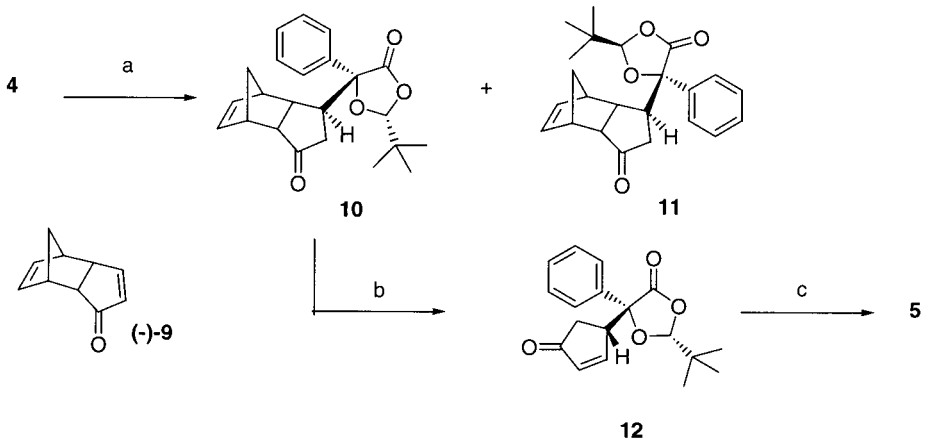
Results and Discussion

Retro-synthetic analysis of **1** suggested two potentially feasible approaches for the diastereoselective synthesis of the key intermediate **5**; (1) diastereoselective hydrogenation of enone **7**, and (2) diastereoselective Michael addition of an enolate of **4** to a cyclopentenone derivative with chiral auxiliaries (Fig. 2).

We first attempted the diastereoselective 1,4-reduction of **7**, which was prepared in 61% yield from **4** by palladium catalyzed oxidation[5] of enol trimethylsilane **8** (Scheme 2). Catalytic hydrogenation of **7** with 10% Pd–C or Rhodium on alumina under a hydrogen atmosphere proceeded in a non-selective manner to give a mixture of **5** and **6** in a ratio of 1.2:1∼1:1.4 (Table 1). In addition, application of some of the reported methods for 1,4-reduction of **7** including DIBAL–CuI,[6] $[(Ph_3P)CuH]_6$–$PhSiH_3$,[7] and Ph_2SiH_2–$Pd(Ph_3P)_4$–$ZnCl_2$[8] systems did not lead to the desired diastereoselectivity. These results indicated that the chirality on the 1,3-dioxolan-4-one moiety may not affect the diastereoselective reduction of the double bond.

Next, we investigated the use of a chirally derived 2-cyclopenten-1-one [e.g. (−)-**9**] as a Michael acceptor in place of 2-cyclopenten-1-one to obtain **5** stereoselectively. (−)-Tricyclo[5,2,1,$0^{2,6}$]deca-4,8-dien-3-one (−)-**9**[9] has been used as a chiral cyclopentenone equivalent for the enantioselective syntheses of various natural products such as (+)-equilenin and (−)-physostigmine.[10] In the previously reported examples, Michael addition of a naphtyl Grignard reagent (2.4 equiv.) to (−)-**9** in the presence of CuI (1.2 equiv.) was reported to produce the *exo*-adduct exclusively,[10] however the conjugate addition of an enolate to this substrate has not been reported.

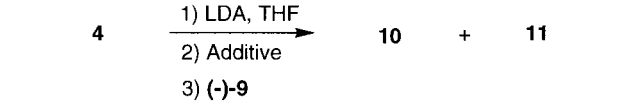
We thus investigated the conjugate addition of the corresponding enolate of **4** to the chiral enone (−)-**9**, paying particular attention to the stoichiometry of the substrate and reagent (Scheme 3). After some experimentation, we found favorable reaction conditions: the lithium enolate of the dioxolane **4** generated by LDA was reacted with 1.1 equiv. of (−)-**9** at −70°C to give Michael adducts **10** and **11** in a ratio of 8:1.[11] Importantly, the desired compound **10** was isolated exclusively (>99% de) by recrystallization of the mixture from hexane–EtOAc in 72% yield from **4**. The stereochemical structure of **10** was elucidated by NOE experiments.[12] The minor isomer **11** was also assigned to be a 5*S*-epimer of **10** by the NOE experiments,[12] indicating that the newly generated asymmetric carbon at the tricyclic ketone moiety was completely stereocontrolled as expected.



Scheme 3. Conditions: (a) LDA, THF, −70°C, then (−)-**9**. (b) 175°C, 1,2-dichlorobenzene. (c) H_2, Pd–C, EtOAc.

It has been reported that chiral or achiral amines aggregating with lithium enolates enhance the selectivity and rate of the corresponding addition reactions.[13] Therefore, the effects of additives on Michael addition of the lithium enolate of **4** were examined in an attempt to increase diastereoselectivity (Table 2). Among the additives tested, tetramethylethylenediamine (TMEDA) gave the best selectivity (**10**:**11**=20:1). This finding suggests that TMEDA coordinating to the enolate may block the undesirable access of (−)-**9** from the *Si* face as well as the *tert*-butyl group, although the structure of this type of aggregate remains unclear.[13]

Table 2. Michael addition of **4** to (−)-**9**



Run	Additive	Ratio of **10** and **11**	Yield (%)[a]
1	None	8:1	72
2	TMEDA	20:1	74
3	Pentamethyldiethylenetriamine	10:1	66
4	Hexamethyltriethylenetetramine	11:1	70

[a] Isolated yields after recrystallization.

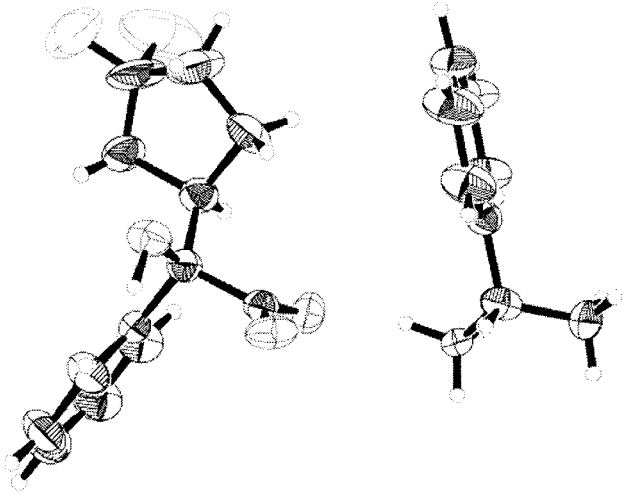


Figure 3. ORTEP drawing (50% ellipsoid) of **1**.

Subsequently, the retrograde Diels–Alder reaction of **10** was accomplished at 175°C in 1,2-dichlorobenzene to produce an enone **12** in 92% yield without any decomposition. The enone **12** was hydrogenated with a catalytic amount of 10% Pd on carbon under a hydrogen atmosphere to yield **5** in 99% yield. Conversion of **5** to **1** was accomplished by difluorination of the ketone moiety using DAST followed by hydrolysis under basic condition as reported previously.[1] The absolute stereochemical structure of **1** was unambiguously determined to be (2*R*,1′*R*) by the X-ray analysis of its (*S*)-phenetylamine salt (Fig. 3).

Conclusion

In summary, we investigated improved synthetic methods for the preparation of **1**, focusing on the diastereoselective synthesis of **5**. As a result, we found that the Michael reaction of an enolate of **4** with a (−)-tricyclo[5,2,1,$0^{2,6}$]-deca-4,8-dien-3-one (−)-**9** proceeded diastereoselectively to yield **10** in 90% de, which was easily converted to the key intermediate **5** in excellent yield. This method may enable us to provide multi-hundred grams of **1** from **4** without chromatographic separation.

Experimental

Melting points were determined with a Yanaco MP micro-melting point apparatus and were not corrected. Proton NMR spectra were obtained on a Varian Gemini-300 with tetramethylsilane as an internal standard. Mass spectrometry was performed with a JEOL JMS-SX 102A. Optical rotations were measured with a Jasco DIP-370 polarimeter. TLC was done with Merck Kieselgel F_{254} pre-coated plates. Silica gel (SiO_2) column chromatography was carried out on Wako gel C-300.

(2*R*,5*R*)-2-*tert*-Butyl-5-(3-oxo-1-cyclopentenyl)-5-phenyl-1,3-dioxolan-4-one (7)

To a solution of (2*R*,5*R*)-2-*tert*-butyl-5-phenyl-1,3-dioxolan-4-one[2] **4** (3.18 g, 14.5 mmol) in THF (150 mL) was dropwise added 1.50 M of lithium diisopropylamide mono-(tetrahydrofuran) in cyclohexane (11.0 mL,

16.5 mmol) at −70°C, and the mixture was stirred at the same temperature for 30 min. To the mixture was added a solution of 2-cyclopenten-1-one (1.40 g, 17.1 mmol) in THF (5 mL) for 10 min, maintaining the temperature below −65°C. After the mixture was stirred for 1 h at −70°C, chlorotrimethylsilane (2.20 mL, 17.3 mmol) was added and the resulting mixture was allowed to warm to −40°C for 2 h. The reaction was quenched by the addition of saturated aqueous NH_4Cl solution at −40°C. The mixture was warmed to room temperature, diluted with H_2O and extracted with EtOAc. The organic layer was washed with H_2O and brine, dried over $MgSO_4$ and concentrated under reduced pressure to give crude **8**. To a solution of crude **8** (6.01 g) in CH_3CN (150 mL) was added *p*-benzoquinone (1.90 g, 17.6 mmol) and palladium acetate (3.30 g, 14.7 mmol) at room temperature. The mixture was stirred for 24 h, concentrated to a small volume and diluted with Et_2O. The insoluble matter was filtered off through a pad of Celite. The filtrate was concentrated under reduced pressure and the residue (**7**:its 5*S*-isomer=9:1) was purified by silica gel column chromatography (hexane–EtOAc, 20:1–10:1 elution) to give a mixture of **7** and its 5*S*-isomer (30:1, 3.50 g). This mixture was further recrystallized to afford **7** (2.65 g, 61%, >98% de) as a white solid: mp 92–94°C (hexane–EtOAc); ^{1}H NMR ($CDCl_3$) δ 1.03 (9H, s), 2.40–2.50 (2H, m), 2.57–2.36 (2H, m), 5.29 (1H, s), 6.44 (1H, m), 7.35–7.50 (3H, m), 7.57–7.71 (2H, m); IR (KBr, cm^{-1}) 1794, 1709; FAB-MS *m/z* 301 $(M+H)^+$; Anal. calcd for $C_{18}H_{20}O_4$: C, 71.98; H, 6.71. Found: C, 71.84; H, 6.66; $[\alpha]_D^{20}=-86.3$ (*c* 1.0, $CHCl_3$).

General procedure for catalytic hydrogenation of 7

To a solution of **7** (51 mg, 0.17 mmol) in EtOH (2 mL) was added 10% palladium on carbon (15 mg, 0.014 mmol), and the mixture was hydrogenated under atmospheric pressure for 2 h. After filtration of the catalyst, the filtrate was concentrated under reduced pressure. After the selectivity ratio of the crude material was determined by ^{1}H NMR (**5**:**6**=1:1.4), the crude material was purified by silica gel column chromatography (hexane–EtOAc, 20:1–10:1 elution) to give a mixture of **5** and **6** (50 mg, 97%). The ^{1}H NMR and MS spectra of **5** and **6** were identical to the reported data.[4]

Other catalytic hydrogenation reactions (run 2–4) were conducted according to this procedure. The yields and selectivity ratios are given in Table 1.

Reduction of 7 with CuI–DIBAL

To a suspension of CuI (200 mg, 1.05 mmol) in THF–HMPA (4:1, 1.0 mL) was added 1.0 M of diisobutyl aluminum hydride in toluene (1.0 mL, 1.0 mmol) at −78°C. After the mixture was stirred for 1 h at the same temperature, **7** (65 mg, 0.22 mmol) was added, and the resulting mixture was allowed to warm to −30°C for 1 h. The reaction was quenched by the addition of 0.5N HCl, and the mixture was extracted with EtOAc. The organic layer was washed with 0.5N HCl, H_2O and brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue (**5**:**6**=1:1.2) was purified by silica gel column chromatography (hexane–EtOAc, 20:1–10:1 elution) to give a mixture of **5** and **6** (50 mg, 76%).

Reduction of 7 with $[(Ph_3P)CuH]_6$ and $PhSiH_3$

To a suspension of $[(Ph_3P)CuH]_6$ (5.0 mg, 0.0025 mmol) in toluene (1.0 mL) were added phenylsilane (0.060 mL, 0.49 mmol) and **7** (95 mg, 0.32 mmol) at room temperature. After stirring for 43 h, the mixture was diluted with Et_2O. The organic layer was washed with saturated aqueous NH_4Cl solution, saturated aqueous $NaHCO_3$ solution and brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue (**5**:**6**=1:1.2) was purified by silica gel column chromatography (hexane–EtOAc, 20:1–10:1 elution) to give a mixture of **5** and **6** (70 mg, 73%).

Pd-catalyzed reduction of 7 with Ph_2SiH_2 and $ZnCl_2$

To a solution of **7** (98 mg, 0.33 mmol) in $CHCl_3$ (2.0 mL) were successively added diphenylsilane (125 mg, 0.49 mmol), zinc chloride (20 mg, 0.15 mmol) and $Pd(Ph_3P)_4$ (10 mg, 0.0087 mmol) at room temperature. After stirring for 46 h, the mixture was washed with saturated aqueous $NaHCO_3$ solution and dried over $MgSO_4$. Evaporation of the solvent gave the crude residue (**5**:**6**=1.1:1), which was purified by silica gel column chromatography (hexane–EtOAc, 20:1–10:1 elution) to afford a mixture of **5** and **6** (71 mg, 72%).

(−)-(1*R*,2*R*,3*S*,6*R*,7*S*)-Tricyclo[5.2.1.0^{2,6}]deca-4,8-dien-3-one [(−)-9]

This was prepared according to the method reported in the literature.[9a] mp 76–77°C (hexane); $[\alpha]_D^{25}=-157.3$ (*c* 1.0, $CHCl_3$); [lit.[9c]: mp 76°C (hexane); $[\alpha]_D^{30}=-158.5$ (*c* 1.0, $CHCl_3$)].

(2*R*,5*R*)-2-*tert*-Butyl-5-[(1*R*,2*R*,3*S*,6*R*,7*S*)-5-oxotricyclo-[5.2.1.0^{2,6}]dec-8-en-3-yl]-5-phenyl-1,3-dioxolan-4-one (10) and (2*R*,5*S*)-2-*tert*-butyl-5-[(1*R*,2*R*,3*S*,6*R*,7*S*)-5-oxotricyclo[5.2.1.0^{2,6}]dec-8-en-3-yl]-5-phenyl-1,3-dioxolan-4-one (11)

To a solution of **4** (21.2 g, 96.5 mmol) in THF (700 mL) was dropwise added 1.50 M of lithium diisopropylamide mono(tetrahydrofuran) in cyclohexane (75.0 mL, 113 mmol) at −70°C, and the mixture was stirred at the same temperature for 30 min. To the mixture was added a solution of (1*S*,2*R*,6*R*,7*R*)-tricyclo[5.2.1.0^{2,6}]dec-4,8-dien-3-one (−)-**9** (15.4 g, 106 mmol) in THF (200 mL), while maintaining the temperature below −65°C, and the resulting mixture was stirred for 1.5 h at −70°C. The reaction was quenched by the addition of saturated aqueous NH_4Cl solution, and the mixture was warmed to room temperature, diluted with H_2O and extracted with EtOAc. The organic layer was washed with H_2O and brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residual solid (**10**:**11**=8:1) was crystallized from hexane–EtOAc to afford **10** (25.5 g, 72%, >98% de) as a white solid: mp 178–180°C (hexane–EtOAc); ^{1}H NMR ($CDCl_3$) δ 0.91 (9H, s), 1.44 (1H, brd, *J*=8.7 Hz), 1.58 (1H, brd, *J*=8.7 Hz), 1.87 (1H, dd, *J*=9.3, 18.6 Hz), 2.25 (1H, dd, *J*=6.9, 18.6 Hz), 2.43 (1H, m), 2.90 (1H, m), 2.93–3.02 (2H, m), 3.17 (1H, m), 5.46 (1H, s),

6.10–6.20 (2H, m), 7.29–7.41 (3H, m), 7.62 (2H, brd, J=8.3 Hz); The NOEs between δ 1.87 (H_b) and δ 2.43 (H_a), δ 2.43 (H_a) and δ 6.10–6.20 (H_e), δ 2.43 (H_a) and δ 7.62 (H_d), δ 2.90 (H_f) and δ 5.46 (H_c) were observed. IR (KBr, cm^{-1}) 1788, 1734; FAB-MS m/z 367 $(M+H)^+$; Anal. calcd for $C_{23}H_{26}O_4$: C, 75.38; H, 7.15. Found: C, 75.43; H, 7.14; $[\alpha]_D^{20}=-65.8$ (c 1.0, $CHCl_3$).

For elucidation of the structure of the minor isomer (**11**), the mother liquid was concentrated, purified by silica gel column chromatography (hexane–EtOAc, 20:1 elution), and recrystallized to afford **11** (2.90 g, 8%) as a white crystalline solid: mp 131–132°C (hexane–EtOAc); ^1H NMR ($CDCl_3$) δ 1.03 (9H, s), 1.28 (1H, brd, J=9.6 Hz), 1.40 (1H, brd, J=9.6 Hz), 2.20 (1H, dd, J=9.6, 18.6 Hz), 2.23 (1H, m), 2.38 (1H, dd, J=6.3, 18.6 Hz), 2.51 (1H, m), 2.80 (1H, m), 2.94 (1H, m), 3.13 (1H, m), 5.11 (1H, s), 6.06 (1H, m), 6.13 (1H, m), 7.36–7.50 (3H, m), 7.56 (2H, brd, J=8.3); The NOEs between δ 2.20 (H_b) and δ 2.51 (H_a), δ 2.51 (H_a) and δ 6.06 (H_e), δ 2.51 (H_a) and δ 7.56 (H_d), δ 5.11 (H_c) and δ 7.56 (H_d) were observed. IR (KBr, cm^{-1}) 1789, 1738; FAB-MS m/z 367 $(M+H)^+$; Anal. calcd for $C_{23}H_{26}O_4$: C, 75.38; H, 7.15. Found: C, 75.39; H, 7.28; $[\alpha]_D^{20}=-176.4$ (c 1.0, $CHCl_3$).

Preparation of 10 (Michael addition of 4 to (−)-9 in the presence of TMEDA)

To a solution of **4** (2.12 g, 9.65 mmol) in THF (70 mL) was dropwise added 1.50 M of lithium diisopropylamide mono(tetrahydrofuran) in cyclohexane (7.45 mL, 11.2 mmol) at −70°C, and the mixture was stirred at the same temperature for 30 min. Subsequently, tetramethylethylenediamine (2.10 mL, 13.9 mmol) was added and the mixture was stirred at −70°C for 1 h. To the mixture was added a solution of (−)-**9** (1.50 g, 10.3 mmol) in THF (20 mL), maintaining the temperature below −65°C, and the resulting mixture was stirred for 1 h at −70°C and allowed to warm to −25°C. The reaction was quenched by the addition of saturated aqueous NH_4Cl solution, and the mixture was warmed to room temperature, diluted with H_2O and extracted with EtOAc. The organic layer was washed with H_2O and brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residual solid (**10**:**11**=20:1) was crystallized from hexane–EtOAc to afford **10** (2.60 g, 74%, >99% de). The diastereomeric excess was determined by HPLC analysis (t_R of **10**: 13.6 min, t_R of **11**: 15.6 min, DAICEL CHIRALCEL OD-RH 0.46×15 cm, 0.5 M $NaClO_4$ aq.: CH_3CN=40:60, flow rate=0.5 ml/min, UV detection 210 nm).

Other reactions using additives (run 3–4) were conducted according to this procedure. The yields and selectivity ratios are given in Table 2.

(2*R*,5*R*)-2-*tert*-Butyl-5-[(1*S*)-4-oxo-2-cyclopentenyl]-5-phenyl-1,3-dioxolan-4-one (12)

A solution of **11** (36.9 g, 101 mmol) in 1,2-dichlorobenzene (1.0 L) was heated at 175°C for 8 h with N_2-flow. The mixture was cooled to room temperature and the white crystal formed was collected by filtration, washed with hexane and dried to afford **12** (18.6 g, 61%). The filtrate was concentrated under reduced pressure and the residue was further crystallized from hexane to give **12** (9.5 g, 31%) as a second crop: mp 93–94°C (hexane–EtOAc); ^1H NMR ($CDCl_3$) δ 0.94 (9H, s), 2.16 (1H, dd, J=6.6, 18.9 Hz), 2.33 (1H, dd, J=2.7, 18.9 Hz), 3.71 (1H, m), 5.21 (1H, s), 6.38 (1H, dd, J=1.8, 5.7 Hz), 7.31–7.49 (3H, m), 7.61–7.76 (3H, m); IR (KBr, cm^{-1}) 1792, 1709; FAB-MS m/z 301 $(M+H)^+$; Anal. calcd for $C_{18}H_{20}O_4$: C, 71.98; H, 6.71. Found: C, 71.79; H, 6.55; $[\alpha]_D^{20}=-94.2$ (c 1.0, $CHCl_3$).

(2*R*,5*R*)-2-*tert*-Butyl-5-[(1*R*)-3-oxocyclopentyl]-5-phenyl-1,3-dioxolan-4-one (5)[4]

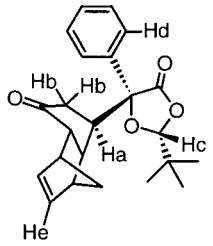
To a solution of **12** (19.1 g, 64.2 mmol) in EtOAc (700 mL) was added 10% palladium on carbon (2.02 g, 1.90 mmol), and the mixture was hydrogenated under atmospheric pressure for 2 h. After filtration of the catalyst, the filtrate was concentrated under reduced pressure. The resultant solid was washed with hexane and dried to afford **5** (16.8 g, 87%). The filtrate was concentrated and purified by silica gel column chromatography (hexane–EtOAc, 20:1–10:1 elution) to give an additional **5** (2.40 g, 12%).

(2*R*,5*R*)-2-*tert*-Butyl-5-[(1*S*,2*S*,3*R*,6*S*,7*R*)-5-oxotricyclo-[5.2.1.0^{2,6}]dec-8-en-3-yl]-5-phenyl-1,3-dioxolan-4-one (13) and (2*R*,5*S*)-2-*tert*-butyl-5-[(1*S*,2*S*,3*R*,6*S*,7*R*)-5-oxotricyclo[5.2.1.0^{2,6}]dec-8-en-3-yl]-5-phenyl-1,3-dioxolan-4-one (14)

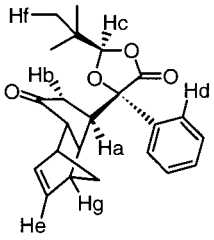
To a solution of **4** (24.6 g, 112 mmol) in THF (800 mL) was dropwise added 1.50 M of lithium diisopropylamide mono(tetrahydrofuran) in cyclohexane (85.0 mL, 128 mmol) at −70°C, and the mixture was stirred at the same temperature for 30 min. To the mixture was added a solution of (1*R*,2*S*,6*S*,7*S*)-tricyclo[5.2.1.0^{2,6}]dec-4,8-dien-3-one (+)-**9** (17.9 g, 123 mmol) in THF (200 mL), maintaining the temperature below −65°C, and the mixture was stirred for 2 h at −70°C. The reaction was quenched by the addition of saturated aqueous NH_4Cl solution, and the mixture was warmed to room temperature, diluted with H_2O and extracted with EtOAc. The organic layer was washed with H_2O and brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residual solid (**13**:**14**=5:1) was recrystallized to afford **13** (25.1 g, 61%, >98% de) as a white solid: mp 162–163°C (hexane–$CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.92 (9H, s), 1.28 (1H, brd, J=8.1 Hz), 1.40 (1H, brd, J=8.1 Hz), 2.13 (1H, m), 2.25–2.32 (2H, m), 2.42 (1H, m), 2.83 (1H, m), 2.91 (1H, m), 3.10 (1H, m), 5.35 (1H, s), 6.02 (1H, m), 6.12 (1H, m), 7.29–7.48 (3H, m), 7.72 (2H, brd, J=8.3 Hz); The NOEs between δ 2.25–2.32 (H_b) and δ 5.35 (H_c), δ 2.25–2.32 (H_b) and δ 2.42 (H_a), δ 2.42 (H_a) and δ 6.02 (H_e), δ 2.42 (H_a) and δ 7.72 (H_d) were observed. IR (KBr, cm^{-1}) 1788, 1743; FAB-MS m/z 367 $(M+H)^+$; Anal. calcd for $C_{23}H_{26}O_4$: C, 75.38; H, 7.15. Found: C, 75.07; H, 7.03; $[\alpha]_D^{20}=+84.0$ (c 1.0, $CHCl_3$).

For elucidation of the structure of the minor isomer (**14**), the mother liquid was concentrated, purified by silica gel column chromatography (hexane–EtOAc, 20:1 elution), and recrystallized to afford **14** (2.69 g, 7%) as a white crystalline solid: mp 133–134.5°C (hexane–EtOAc); ^1H NMR ($CDCl_3$) δ 1.05 (9H, s), 1.39 (1H, brd, J=8.4 Hz), 1.54 (1H, brd, J=8.4 Hz), 1.90 (1H, dd, J=10.7, 19.5 Hz), 2.15 (1H, dd, J=5.7, 19.5 Hz), 2.48 (1H, m), 2.93 (1H, m), 2.97–3.06

(2H, m), 3.19 (1H, m), 5.07 (1H, s), 6.11 (1H, m), 6.21 (1H, m), 7.30–7.46 (3H, m), 7.47 (2H, brd, J=8.1 Hz); The NOEs between δ 1.05 (H_f) and δ 2.93 (H_g), δ 1.90 (H_b) and δ 2.48 (H_a), δ 2.48 (H_a) and δ 6.21 (H_e), δ 2.48 (H_a) and δ 7.47 (H_d), δ 5.07 (H_c) and δ 7.47 (H_d) were observed. IR (KBr, cm^{-1}) 1794, 1732; FAB-MS m/z 367 $(M+H)^+$; Anal. calcd for $C_{23}H_{26}O_4$: C, 75.38; H, 7.15. Found: C, 75.34; H, 7.23; $[\alpha]_D^{20}$=+8.4 (c 1.0, $CHCl_3$).



13



14

(2*R*,5*R*)-2-*tert*-Butyl-5-[(1*S*)-3-oxocyclopentyl]-5-phenyl-1,3-dioxolan-4-one (6)

A solution of **13** (25.1 g, 68.5 mmol) in 1,2-dichlorobenzene (500 mL) was heated at 175°C for 5 h with N_2-flow. The mixture was allowed to cool to room temperature and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane–EtOAc, 10:1 elution) to give (2*R*,5*R*)-2-*tert*-butyl-5-[(1*R*)-4-oxo-2-cyclopentenyl]-5-phenyl-1,3-dioxolan-4-one (19.5 g, 95%) as a white solid: mp 122.5–124°C (hexane–EtOAc); ^{1}H NMR ($CDCl_3$) δ 0.90 (9H, s), 2.27 (1H, dd, J=1.5, 18.9 Hz), 2.49 (1H, dd, J=6.6, 18.9 Hz), 3.67 (1H, m), 5.44 (1H, s), 6.26 (1H, m), 7.30–7.48 (4H, m), 7.60–7.72 (2H, m); IR (KBr, cm^{-1}) 1792, 1716; FAB-MS m/z 301 $(M+H)^+$; Anal. calcd for $C_{18}H_{20}O_4$: C, 71.98; H, 6.71. Found: C, 72.00; H, 6.76; $[\alpha]_D^{20}$=+151 (c 1.0, $CHCl_3$).

To a solution of (2*R*,5*R*)-2-*tert*-butyl-5-[(1*R*)-4-oxo-2-cyclopentenyl]-5-phenyl-1,3-dioxolan-4-one (8.03 g, 26.8 mmol) in EtOAc (300 mL) was added 10% palladium on carbon (1.05 g, 0.987 mmol) and the mixture was hydrogenated under atmospheric pressure for 2 h. After filtration of the catalyst, the filtrate was concentrated and purified by silica gel column chromatography (hexane–EtOAc, 20:1–10:1 elution) to give **6** (7.84 g, 97%) as a white solid.

X-Ray crystallographic data of the (*S*)-phenetylamine salt of 1

A colorless plate crystal having approximate dimensions of 1.00×0.200×0.080 mm was mounted on a glass fiber. All data were collected on a Rigaku AFC7R single crystal diffractometer, using Cu-Kα radiation (λ=1.5418 Å), $\omega-2\theta$ scans, to a maximum 2θ value of 120.0°. $C_{21}H_{25}F_2NO_3$, M=377.43, monoclinic, a=12.430(2) Å, b=5.743(1) Å, c=14.608(1) Å, V=1006.5(5) Å^3, space group $P2_1$ (#4), Z=2, D_{calc}=1.245 g/cm^3, μ=7.93 cm^{-1}. A total of 1611 reflections were collected. All data were corrected for Lorentz and polar factors. All calculations were performed using the teXsan [Crystal Structure Analysis Package, Molecular Structure Corporation (1985 and 1992)]. The structure was solved by a direct method. All non-hydrogen atoms were refined anisotropically. Hydrogen atoms were included but not refined. The final cycle of full-matrix least-squares refinement was based on 1276 observed reflections [$I>3.00\sigma(I)$] and 245 variable parameters and was converged (largest parameter shift was 0.01 times its esd) with unweighted and weighted agreement factors of R=0.064 R_W=0.055. The maximum and minimum peaks on the final difference Fourier map corresponded to 0.34 and −0.24 e$^-$/Å^3, respectively.

Detailed data have been deposited with the Cambridge Crystallographic Data Centre (CCDC) as the reference number 149832.

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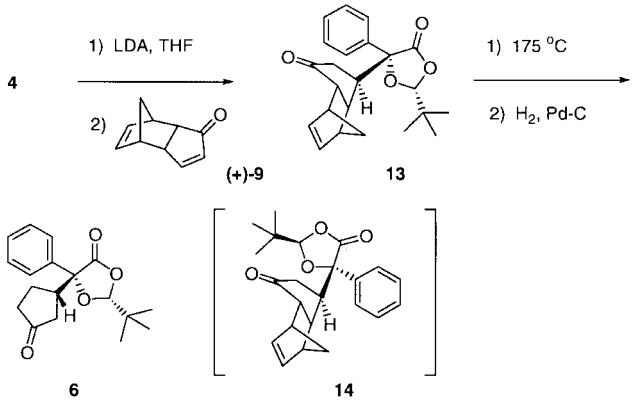
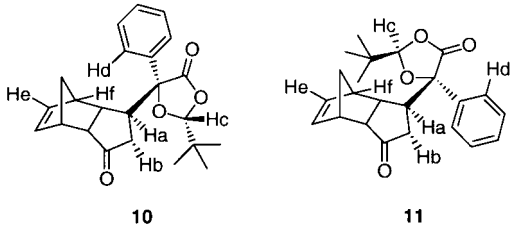
11. When (+)-4,8-tricyclo[5,2,1,0^{2,6}]decadien-3-one (+)-**9** was used in this reaction, the diastereomer **13** was predominantly produced (**13**:**14**=5:1). The adduct **13**, isolated in 61% yield by recrystallization of the mixture, was submitted to retrograde Diels–Alder reaction. Subsequent hydrogenation gave **6** in 92% yield from **13**.



12. The NOEs between H_a and H_b, H_a and H_d, H_a and H_e, and H_c and H_f in **10** were observed. By contrast, the NOEs between H_a and H_b, H_a and H_d, H_a and H_e, and H_c and H_d in **11** were observed.



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