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Studies on 1,2,3,4-Tetrahydroisoquinolines. V.[1] A Convenient Synthesis of (±)-5,7-Dihydroxy-1-(3,4,5-trimethoxybenzyl)-1,2,3,4-tetrahydroisoquinoline (Racemic TA-073)

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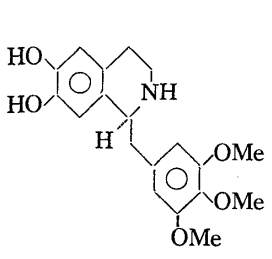
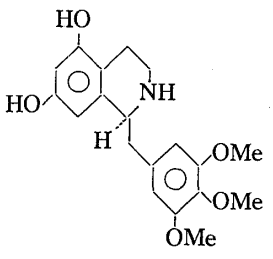
A convenient synthetic route to (±)-5,7-dihydroxy-1-(3,4,5-trimethoxybenzyl)-1,2,3,4-tetrahydroisoquinoline (racemic TA-073), an orally active bronchodilator, through the cyclization of the amine **4** or its *N*-acyl derivative (**10b, c**) is presented. Catalytic reduction of **4** over 10% Pd-C in EtOH–H_2O in the presence of oxalic acid (6 eq) afforded racemic TA-073 in 65% yield. The acid-catalyzed reaction of **10b, c** was also investigated. Cyclization of **10b, c** with 1 N HCl (1 eq) in THF gave the corresponding *N*-acyl enamine **12b, c** in quantitative yield. Further treatment of **12b** with conc. HCl in THF afforded the pavine derivative **14** in 80% yield. Cyclization of **10b** with neat HCOOH, however, resulted in the formation of the isopavine derivative **11b** in 80% yield. This result parallels the reported observation by McDonald *et al.*

Keywords——1,2,3,4-tetrahydroisoquinolines; β-adrenoceptor activity; bronchodilator; oral efficacy; convenient synthesis of racemic TA-073; acid-catalyzed cyclization; Grignard reaction; pavine derivative; isopavine derivative

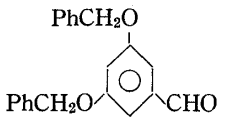
In the preceding paper,[1] we reported that (*S*)-(—)-5,7-dihydroxy-1-(3,4,5-trimethoxybenzyl)-1,2,3,4-tetrahydroisoquinoline (TA-073), a positional isomer of trimetoquinol (TMQ) with respect to its 6,7-dihydroxyl groups, exhibits potent β-adrenoceptor activity (Chart 1). This compound is currently under clinical trials as an orally active bronchodilator.[2] Previously, recemic TA-073 was prepared from the aldehyde **1** *via* several steps[3]; the Barbier reaction[4] of the quaternary salt **2** was involved as a key step. In this paper, we describe a more convenient synthetic method for racemic TA-073 through the cyclization of the amine **4** or its *N*-acyl derivatives (**10b, c**). Bobbitt *et al.* reported that the addition of MeMgI to *N*-benzylideneaminoacetaldehyde diethyl acetals followed by acid-catalyzed cyclization and catalytic reduction gave 1-methyl-1,2,3,4-tetrahydroisoquinoline derivatives *via* the 4-hydroxy intermediates in good yields.[5a,b]



TMQ



TA-073



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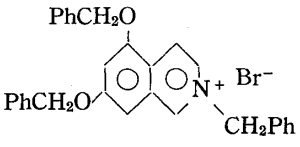

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Chart 1

Treatment of the imine **3**,[6] prepared from the aldehyde **1** in the usual manner, with 3,4,5-trimethoxybenzyl magnesium chloride in THF gave the Grignard product **4** in 87% yield.[7] We examined the acid catalyzed-cyclization of the amine **4** next. It is well known that the acid-catalyzed reaction of 4-hydroxy-1,2,3,4-tetrahydroisoquinolines having an electron-rich arylmethyl group at the 1-position readily gives a cyclized product such as an isopavine- or pavine-type alkaloid.[8] As expected, the reaction of **4** with 6 N HCl (8.5 eq) in refluxing MeOH for 9 h gave the isopavine-type product **8** and the pavine-type product **9** in 43% and 10% yields, respectively, *via* the intermediates **6** and **7**. To obtain racemic TA-073 without formation of these doubly cyclized products, therefore, the acid-catalyzed cyclization of **4** was carried out under catalytic reduction conditions. Catalytic reduction of **4** over 10% Pd-C in EtOH–H_2O (3:2, v/v) in the presence of oxalic acid (6 eq) at 60—70 °C for 48 h gave the desired product (racemic TA-073) in 65% yield (Chart 2). Thus, racemic TA-073 could be obtained through a much shorter route than the previous method.

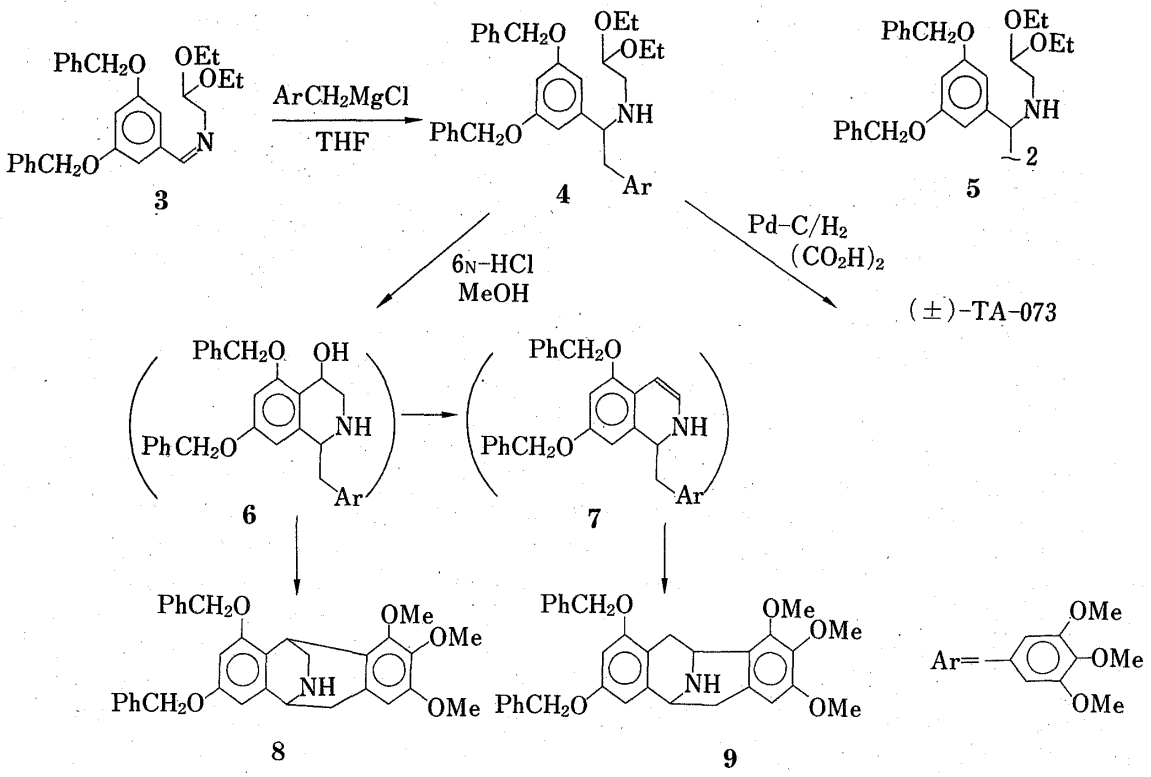
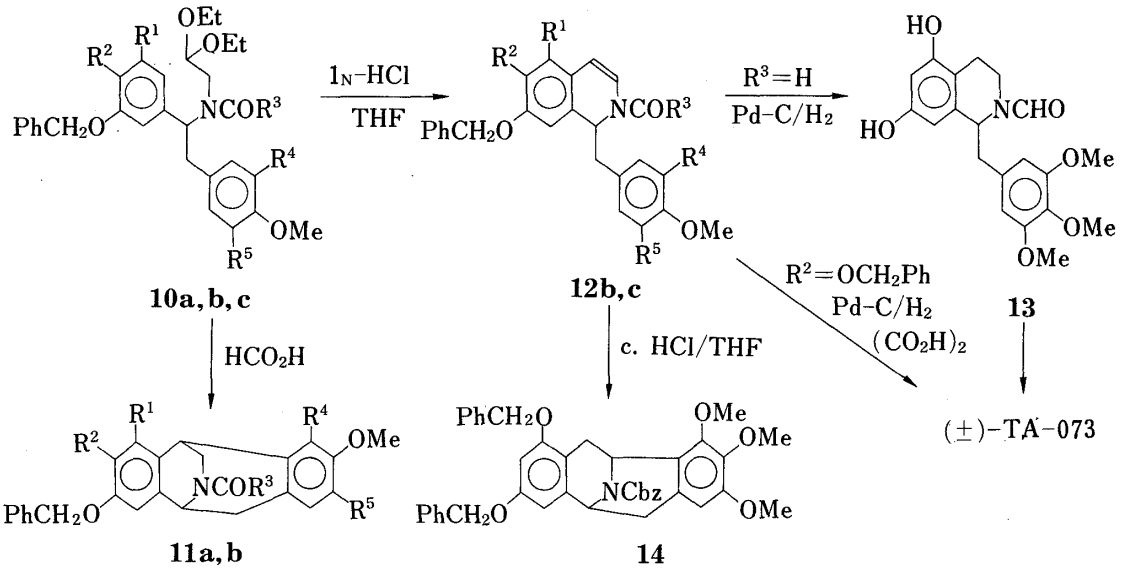


Chart 2

We also examined the acid-catalyzed reaction of the *N*-acyl derivatives (**10b, c**) of **4** (Chart 3). Recently, McDonald *et al.* reported that the acid-catalyzed cyclization of the urethane acetal **10a** in HCO_2H proceeds smoothly to give the isopavine-type product **11a** in quantitative yield.[9] A similar treatment of the *N*-benzyloxycarbonyl derivative **10b** in HCO_2H gave the isopavine-type derivative **11b** in good yield. When treated with 1 N HCl (1 eq) in refluxing THF for 0.5 h, however, **10b, c** gave exclusively the *N*-acyl enamines **12b, c** in quantitative yields. Catalytic reduction of **12b** over 10% Pd-C in MeOH–THF (3:1, v/v) in the presence of oxalic acid (6 eq) gave racemic TA-073 in 73% yield. Reduction of **12c** also proceeded readily to give the *N*-formyl compound **13**, which in turn was hydrolyzed with aqueous H_2SO_4 to give racemic TA-073 in 76% yield.

Finally, it is worth noting that treatment of the *N*-acyl enamine **12b** with conc. HCl in THF at room temperature resulted in the exclusive formation of the pavine-type compound **14** in good yield. Thus, the products of the acid-catalyzed reaction of **10** changed dramatical-



a: $R^1=R^4=H$, $R^2=OMe$, $R^3=OEt$, $R^5=OCH_2Ph$
b: $R^1=R^3=OCH_2Ph$, $R^2=H$, $R^4=R^5=OMe$
c: $R^1=OCH_2Ph$, $R^2=R^3=H$, $R^4=R^5=OMe$

Chart 3

ly with very slight changes in the acidic conditions, and an isoquinoline, pavine, or isopavine derivative can be obtained selectively by the choice of appropriate conditions. This finding should be useful for the synthesis of these alkaloids.

Experimental

Melting points are uncorrected. IR spectra were recorded with a Hitachi IR-215 spectrometer, NMR spectra with a JEOL-PMX 60 or PS-100 spectrometer (using TMS as an internal standard), and mass spectra with a Hitachi RMU-6M spectrometer. Thin-layer chromatography (TLC) and column chromatography were carried out on silica gel 60F-254 (Merck) and 60 (70—230 mesh ASTM) (Merck), respectively.

***N*-[*α*-(3,5-Dibenzyloxyphenyl)-*β*-(3,4,5-trimethoxyphenyl)]ethylaminoacetaldehyde Diethyl Acetal (4)**——i) Grignard Method: A solution of 3,4,5-trimethoxybenzyl chloride (52 g, 240 mmol) in THF (250 ml) was added to a stirred suspension of Mg[10] (24.3 g, 1 g-atom) in THF (200 ml) under cooling below 15°C for 15 min, and stirring was continued at 3°C for 40 min. A solution of the Schiff base 3[6] (21.7 g, 50 mmol) in THF (60 ml) was then added at 0°C over 0.5 h, and the whole was stirred at room temperature overnight. The reaction mixture was concentrated *in vacuo*, then treated with 10% NH_4Cl aq. and extraction was carried out with AcOEt. The AcOEt extracts were washed with brine, dried (Na_2SO_4), and concentrated. The residue was dissolved in hot EtOH and the solution was allowed to cool. The resulting crystals were collected by filtration to afford 3,3′,4,4′,5,5′-hexamethoxybibenzyl[3] (12 g), mp 138—139°C. The filtrate was converted to the oxalate and crystallized from AcOEt–Et_2O (1: 2, v/v) to give **4**·oxalate (30.6 g, 87%) as colorless needles, mp 108—110°C. IR ν_{max}^{Nujol} cm^{-1}: 1750, 1660. *Anal.* Calcd for $C_{37}H_{45}NO_7 \cdot C_2H_2O_4$: C, 66.37; H, 6.71; N, 1.98. Found: C, 66.35; H, 6.69; N, 1.94. **4** (free base): colorless needles (from EtOH–H_2O), mp 74—75°C. MS (*m/e*): 615 (M^+), 434, 181. NMR ($CDCl_3$) δ: 1.10 and 1.12 (6H, 2t, $J=7$ Hz, $-OCH_2\underline{C}H_3 \times 2$), 1.75 (1H, s, NH), 3.80 (9H, s, OMe×3), 4.48 (1H, t, $J=6$ Hz, $-C\underline{H}(OEt)_2$), 5.00 (4H, s, $-O\underline{C}H_2C_6H_5 \times 2$), 6.32 (2H, s, H(2′) and H(6′)), 6.49 (1H, d, $J=2$ Hz, H(4)), 6.59 (2H, d, $J=2$ Hz, H(2) and H(6)), 7.2—7.4 (10H, m, $-C_6\underline{H}_5 \times 2$).

ii) Barbier Method: The Schiff base 3 (4.77 g, 10 mmol) was added to a stirred suspension of Mg[10] (730 mg, 30 mg-atom) in THF (20 ml), then a solution of 3,4,5-trimethoxybenzyl chloride (3.25 g, 15 mmol) in THF (30 ml) was added, and the whole was refluxed for 1 h. After cooling, the reaction mixture was treated with 10% NH_4Cl aq. and extracted with AcOEt. The AcOEt extracts were washed with H_2O, dried (Na_2SO_4), and concentrated. The residue was converted to the oxalate, which was crystallized from EtOH–Et_2O to afford **4**·oxalate (4.22 g, 60%), mp 100—105°C. The product remaining in the mother liquor was converted to free base and purified by column chromatography. Elution with AcOEt–hexane (1: 1, v/v) gave the dimer **5** (251 mg, 5.8%), which was recrystallized from AcOEt–hexane to afford colorless needles, mp 140—140.5°C. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3340. MS (*m/e*): 868 (M^+), 777 (M^+-91), 434 (base), 388, 343, 342, 298,

297. NMR ($CDCl_3$) δ: 0.99 and 1.05 (12H, 2t, J=7 Hz, $-OCH_2C\underline{H}_3\times4$), 1.60 (2H, s, NH×2), 2.2—2.5 (4H, m, $-NCH_2\times2$), 3.33 and 3.36 (8H, 2q, J=7 Hz, $-OC\underline{H}_2CH_3\times4$), 3.56 (2H, s, $ArC\underline{H}N-\times2$), 4.36 (2H, m, $-C\underline{H}(OEt)_2\times2$), 4.96 (8H, s, $-OC\underline{H}_2C_6H_5\times4$), 6.52 (2H, d, J=2 Hz), 6.63 (4H, d, J=2 Hz), 7.1—7.5 (20H, m, $-C_6H_5\times4$). *Anal.* Calcd for $C_{54}H_{64}N_2O_8$: C, 74.63; H, 7.42; N, 3.22. Found: C, 74.58; H, 7.48; N, 3.24. The second eluate with the same solvent give **4** (920 mg, 15%).

Cyclization of 4 to Isopavine (8) and Pavine (9)——A mixture of **4**·oxalate (2.5 g, 3.55 mmol), 6 N HCl (5 ml), and MeOH (15 ml) was refluxed for 9 h. After removal of the solvent, the residue was converted to the free base and separated by column chromatography. Elution with $CHCl_3$–MeOH (20: 1, v/v) gave the pavine (**9**) (185 mg, 10%) as an oil. NMR ($CDCl_3$) δ: 2.03 (1H, s, NH), 2.72 (1H, d, J=16 Hz), 2.89 (1H, s), 2.91 (1H, d, J=6 Hz), 3.26 (1H, d-d, J=6 and 16 Hz), 3.67, 3.73, and 3.88 (9H, 3s, OMe×3), 4.30 (1H, d, J=6 Hz), 4.61 (1H, d, J=6 Hz), 4.87 and 4.92 (4H, 2s, $-OC\underline{H}_2C_6H_5\times2$), 7.1—7.4 (10H, m, $-C_6H_5\times2$). **9**·HCl: colorless prisms (from MeOH), mp 252—254°C (dec.). IR ν_{max}^{Nujol} cm^{-1}: 3550, 3425. MS (*m/e*): 523 (M^+), 522, 432, 313, 220, 91. *Anal.* Calcd for $C_{33}H_{33}NO_5\cdot HCl\cdot1/2H_2O$: C, 69.65; H, 6.20; N, 2.46. Found: C, 69.75; H, 6.07; N, 2.63. The second eluate with the same solvent gave the isopavine (**8**) (790 mg, 43%) as an oil. NMR ($CDCl_3$) δ: 2.16 (1H, s, NH), 3.60, 3.69, and 3.76 (9H, 3s, OMe×3), 4.1—4.2 (1H, m), 4.96 and 4.98 (4H, 2s, $-OC\underline{H}_2C_6H_5\times2$), 5.05—5.15 (1H, m), 6.31 (1H, s), 6.44 and 6.48 (2H, 2d, J=2.5 Hz), 7.1—7.5 (10H, m, $-C_6H_5\times2$). **8**·HCl: colorless needles (from MeOH–Et_2O), mp 249—252°C (dec.). IR ν_{max}^{Nujol} cm^{-1}: 3205, 3150. MS (*m/e*): 523 (M^+), 494, 432, 403. *Anal.* Calcd for $C_{33}H_{33}NO_5\cdot HCl$: C, 70.77; H, 6.12; N, 2.50. Found: C, 70.42; H, 6.21; N, 2.56.

***N*-Benzyloxycarbonyl-[*α*-(3,5-dibenzyloxyphenyl)-*β*-(3,4,5-trimethoxyphenyl)]ethylaminoacetaldehyde Diethyl Acetal (10b)**——A solution of benzyloxycarbonyl chloride (890 mg, 5.2 mmol) in $CHCl_3$ (5 ml) was added to a stirred mixture of **4** (2.46 g, 5 mmol), $NaHCO_3$ (840 mg, 10 mmol), $CHCl_3$ (50 ml), and H_2O (30 ml) under cooling below 2°C. The mixture was stirred at 2°C for 0.5 h, and then at room temperature for 1 h. The $CHCl_3$ layer was separated, washed successively with sat. $NaHCO_3$aq. and sat. brine, dried (Na_2SO_4), and concentrated. The residue was purified by column chromatography (AcOEt–hexane, 1: 4, v/v) to afford **10b** (3.13 g, 84%) as a colorless oil. IR ν_{max}^{liq} cm^{-1}: 1690. MS (*m/e*): 749 (M^+), 704, 568, 478, 347, 181. NMR (DMSO-d_6) δ: 0.98 (6H, t, J=7 Hz, $-OCH_2C\underline{H}_3\times2$), 3.61 (3H, s, OMe), 3.67 (6H, s, OMe×2), 5.04 (6H, s, $-OC\underline{H}_2C_6H_5\times2$, $NCO_2C\underline{H}_2C_6H_5$), 6.5—6.8 (3H, m), 7.30 (5H, s, $-C_6H_5$), 7.39 (10H, s, $-C_6H_5\times2$).

[*α*-(3,5-Dibenzyloxyphenyl)-*β*-(3,4,5-trimethoxyphenyl)]-*N*-formyl-ethylaminoacetaldehyde Diethyl Acetal (10c)——A mixture of **4**·oxalate (705 mg, 1 mmol) and CH_2Cl_2 (4 ml) was added to a stirred mixture of HCO_2Na (200 mg) and excess HCO_2Ac, prepared from 99% HCO_2H (550 mg) and Ac_2O (1.02 g) at 50°C for 20 min, and the whole was stirred at room temperature for 1 h. The reaction mixture was treated with $NaHCO_3$aq. and extraction was carried out with AcOEt. The AcOEt extracts were washed successively with sat. $NaHCO_3$ aq. and sat. brine, dried (Na_2SO_4), and concentrated *in vacuo* to give **10c** (640 mg, 100%) as a colorless oil. IR ν_{max}^{Nujol} cm^{-1}: 1660 (NCHO). MS (*m/e*): 643 (M^+). NMR ($CDCl_3$) δ: 0.9—1.4 (6H, m, $-OCH_2C\underline{H}_3\times2$), 3.77 and 3.81 (9H, 2s, OMe×3), 4.97 and 5.00 (4H, 2s, $-OC\underline{H}_2C_6H_5\times2$), 6.2—6.7 (5H, m, ArH×5), 7.37 (10H, s, $-C_6H_5\times2$), 8.08 and 8.24 (1H, 2s, CHO).

***N*-Benzyloxycarbonyl-5,7-dibenzyloxy-1-(3,4,5-trimethoxybenzyl)-1,2-dihydroisoquinoline (12b)**——A solution of **10b** (375 mg, 0.5 mmol) and 1 N HCl (0.5 ml) in THF (4 ml) was refluxed for 0.5 h. The mixture was treated with $NaHCO_3$ aq., and extraction was carried out with AcOEt. The AcOEt extracts were washed successively with $NaHCO_3$ aq., H_2O, and sat. brine, dried (Na_2SO_4), and concentrated *in vacuo* to give **12b** (325 mg, 100%) as an oil, which was crystallized from MeOH to give colorless needles, mp 120—121.5°C. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1700. MS (*m/e*): 657 (M^+). *Anal.* Calcd for $C_{41}H_{39}NO_7$: C, 74.87; H, 5.98; N, 2.13. Found: C, 74.78; H, 5.96; N, 2.07.

5,7-Dibenzyloxy-*N*-formyl-1-(3,4,5-trimethoxybenzyl)-1,2-dihydroisoquinoline (12c)——**10c** (322 mg, 0.5 mmol) was treated as described above for the preparation of **12b** to give **12c** (280 mg, 100%) as a pale yellow oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1680. MS (*m/e*): 551 (M^+).

Conversion of 10b to Isopavine (11b) in HCO_2H——A 90% HCO_2H solution (5 ml) was added to **10b** (500 mg, 0.67 mmol) with ice-cooling and the mixture was stirred at room temperature for 1.5 h. The reaction mixture was treated with H_2O, made alkaline with $NaHCO_3$, and extracted with $CHCl_3$. The $CHCl_3$ extracts were washed with sat. brine, dried ($MgSO_4$), and concentrated to leave **11b** (350 mg, 80%) as a colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1680. MS (*m/e*): 657 (M^+), 566, 522, 494, 403. NMR ($CDCl_3$) δ: 3.62, 3.72, and 3.80 (9H, 3s, OMe×3), 4.98 (4H, s, $-OC\underline{H}_2C_6H_5\times2$), 6.28 (1H, s, ArH), 6.49 (2H, s, ArH×2), 7.27 and 7.35 (15H, 2s, $-C_5H_5\times3$).

Conversion of 12b to Pavine (14)——A mixture of **12b** (20 mg) and conc. HCl (3 drops) in THF (1 ml) was stirred at room temperature for 22.5 h. The reaction mixture was neutralized with $NaHCO_3$ and extracted with $CHCl_3$. The $CHCl_3$ extracts were washed with sat. brine, dried ($MgSO_4$), and concentrated. The residue was crystallized from AcOEt–hexane to afford **14** (16 mg, 80%) as colorless needles, mp 159—160°C. IR ν_{max}^{Nujol} cm^{-1}: 1700. MS (*m/e*): 657 (M^+), 566, 522, 340, 220, 91. NMR ($CDCl_3$) δ: 3.71, 3.76, and 3.92 (9H, 3s, OMe×3), 4.89, 4.94, and 5.12 (6H, 3s, $-OCH_2C_6H_5\times2$, $-NCO_2CH_2C_6H_5$), 6.23 (1H, s), 6.35 (2H, s), 7.27 (15H, s, $-C_6H_5\times3$). *Anal.* Calcd for $C_{41}H_{39}NO_7$: C, 74.87; H, 5.98; N, 2.13. Found: C, 74.52; H, 5.98; N, 2.13.

Preparation of (±)-TA-073——i) A solution of **4** (1.85 g, 3 mmol) and oxalic acid (1.62 g, 18 mmol) in EtOH–H_2O (3: 2, v/v) (30 ml) was hydrogenated over 10% Pd-C (0.75 g) at 3.0 atmospheres pressure and at 60—70°C for 48 h. After removal of the catalyst by filtration, the filtrate was converted to the sulfate, which was crystallized from EtOH–Et_2O to give (±)-TA-073·1/2H_2SO_4–EtOH[6] (858 mg, 65%) as colorless prisms, mp 206—209°C (dec.).

ii) Treatment of **4**·oxalate (2.12 g, 3 mmol) with benzyloxycarbonyl chloride (600 mg, 3.54 mmol) as described above gave **10b** (2.23 g) as an oil. The crude **10b** was treated with 1 N HCl (3 ml) in THF (20 ml) under reflux for 0.5 h to afford **12b** as an oil. Without purification, the crude **12b** was hydrogenated over 10%Pd-C (0.66 g) in MeOH (20 ml) and THF (10 ml) containing oxalic acid (1.62 g, 18 mmol) at 3.7 atmospheres pressure and at 60—70°C for 18 h. Work-up as described above yielded (±)-TA-073·1/2H_2SO_4·EtOH (962 mg, 73%) as colorless prisms, mp 206—209°C (dec.).

iii) A solution of **12c** (642 mg, 1 mmol) in THF (14 ml) and H_2O (6 ml) was hydrogenated over 10% Pd-C (0.25 g) at 3.3 atmospheres pressure and at 60°C for 22 h. After removal of the catalyst by filtration, the filtrate was concentrated *in vacuo* to leave an oily residue of **13**, which was hydrolyzed with 10% H_2SO_4 aq. (4.9 ml) and EtOH (13 ml) under reflux for 30 h to give (±)-TA-073·1/2H_2SO_4·EtOH (336 mg, 76%) as colorless prisms, mp 206—209°C (dec.). An analytical sample of **13**, which showed two spots on TLC ($CHCl_3$–MeOH, 9: 1, v/v) corresponding to the two rotomers,[11] was obtained by crystallization from EtOH–hexane as colorless prisms, mp 192—193°C. IR ν_{max}^{Nujol} cm^{-1}: 3350, 3140, 1650. MS (*m/e*): 373 (M^+), 192 (M^+-181), 181. NMR (DMSO-d_6) δ: 2.80—3.20 (4H, m), 3.63, 3.70, and 3.74 (9H, 3s, OMe×3), 6.1—6.3 (2H, m), 6.45 and 6.53 (2H, 2s, ArH×2), 7.54 and 7.97 (1H, 2s, CHO). The ratio of the rotomers in this sample was ~1: 2. *Anal.* Calcd for $C_{20}H_{23}NO_6$: C, 64.33; H, 6.21; N, 3.75. Found: C, 64.20; H, 6.17; N, 3.72.

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References and Notes

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