A Convenient Synthesis of Dengibsin

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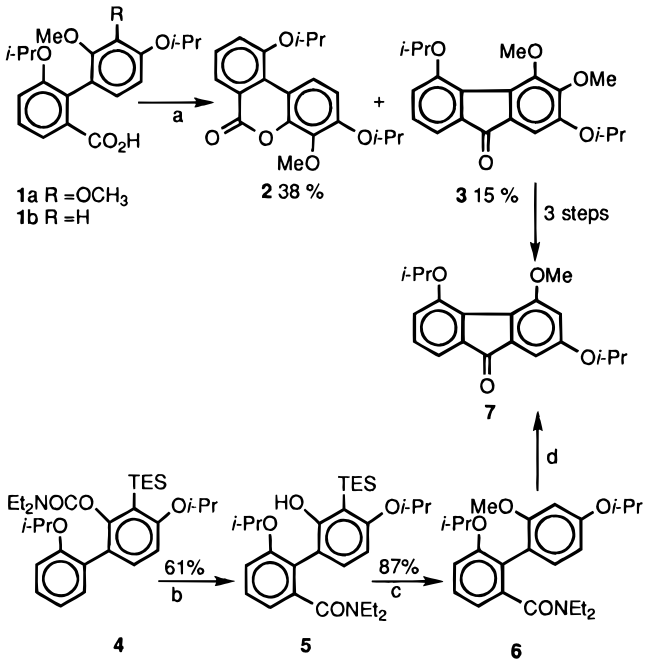
Received January 22, 1996

Dengibsin is a natural product isolated from the Indian orchid *Dendrobium gibsonii* Lindl.[1] A review of the literature revealed total syntheses by Sargent[2] and Snieckus et al.[3] (Scheme 1). Evaluation of these syntheses showed they were unsuitable for the preparation of gram quantities of **13**. Both approaches used fluorenone **7** as a common intermediate. Sargent utilized a Friedel−Crafts closure of intermediate **1a** to give dibenzopyran **2** and fluorenone **3** in 38% and 15% yield, respectively. The minor product **3** was converted in three steps to fluorenone **7** in low overall yield. Snieckus avoided the problem of dibenzopyran formation[4] by the elegant use of a remote anionic Fries rearrangement of carbamate **4** to give **5**.[3] Two additional steps gave the amide **6**, which underwent an anionic Friedel−Crafts reaction to give **7**. While an improvement over the previous synthesis, this process required eight steps to obtain intermediate **7** and ultimately produced dengibsin **13** in only12% overall yield.

In this note we describe a new synthesis of dengibsin in which the conversion of acid **1b** to amide **6** is the key step to prepare **13** in high overall yield (Scheme 2). For the efficient construction of the biphenyl amide **6**, we chose the coupling of an α-alkoxyoxazoline with a suitably substituted aryl Grignard reagent.[5] Thus, alkylation of phenol **8**[6] with isopropyl iodide using K_2CO_3 gave aryl bromide **9**. Reaction of the Grignard reagent derived from **9** with oxazoline **10**[2,7] at 50 °C in THF gave the biphenyl derivative **11**. This was converted to the quaternary salt **12** using MeI in DMSO. Hydrolysis of **12** under basic conditions gave acid **1b**. We thought that intermediate amide **6** could be prepared in high yield from acid **1b** by using a reagent that would avoid dibenzopyran formation.[4] (Benzotriazol-1-yloxy)tris(pyrrolidino)phosphonium hexafluorophosphate (PyBOP)[8,9] when used as the coupling reagent produced the expected amide with no trace of the unwanted dibenzopyran. Thus, acid **1b** was condensed with diethylamine at ambient temperature using PyBOP and DIEA to give the requisite amide **6** in 85% yield. As previously reported,[2] ring closure of **6** with LDA in THF gave **7**, which was deprotected to give dengibsin **13**.

Scheme 1[a]



[a] (a) TFAA, rt, 6.5 h; (b) 3 equiv of LDA, THF, recycle; (c) (1) MeI, K_2CO_3; (2) TFA, reflux; (d) 2.5 equiv of LDA, THF, 0 °C to rt.

In conclusion, we have developed a convenient six-step route to dengibsin in 26% overall yield from readily prepared intermediates.

Experimental Section

Melting points are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were obtained at 300 and 75 MHz, respectively. Chemical shifts are reported in δ values relative to Me_4Si ($\delta = 0.00$) as an internal standard for ^{1}H NMR spectra.

1-Bromo-2-methoxy-4-(1-methylethoxy)benzene (9). To a stirred suspension of **8**[6] (2.03 g, 10 mmol) and K_2CO_3 (1.38 g, 10 mmol) in 2-butanone (70 mL) at ambient temperature under argon was added dropwise isopropyl iodide (2.21 g, 13.3 mmol). The resulting mixture was heated and stirred under reflux for 17 h. The mixture was allowed to cool to ambient temperature, then filtered, and concentrated by evaporation of solvent. The residue was partitioned between Et_2O and H_2O. The Et_2O layer was extracted with 5% NaOH (2 × 50 mL), washed with brine, and dried over $MgSO_4$. The solvent was evaporated and the resulting residue purified by flash chromatography[10] (5% EtOAc/hexane) to afford the desired compound as a pale yellow oil: 2.13 g (87%); UV (MeOH) $\lambda_{max} = 283$ nm, $\epsilon = 9510$; ^{1}H NMR ($CDCl_3$) δ 7.38 (δ, 1H, $J = 8.6$ Hz), 6.47 (1H, d, $J = 2.7$ Hz), 6.38 (1H, dd, $J = 8.5$, 2.7 Hz), 4.5 (1H, hept, $J = 6.3$ Hz), 3.85 (3H, s), 1.33 (6H, d, $J = 6.3$ Hz); ^{13}C NMR ($CDCl_3$) δ 158.4, 156.6, 133.0, 107.7, 102.0, 101.8, 70.3, 56.0, 21.9. Anal. Calcd for $C_{10}H_{13}BrO_2$: C, 49.00; H, 5.35. Found: C, 48.87; H, 5.12.

4,5-Dihydro-2-[2,3-bis(1-methylethoxy)-1-phenyl]-4,4-dimethyloxazole (10). NaH (8.25 g, 60%, 0.205 mol) was added portionwise to a stirred solution of 2-amino-2-methylpropanol

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(2) (a) Sargent, M. V. *J. Chem Soc., Perkin Trans. 1* **1987**, 2553−2563. (b) To the best of our knowledge, compound **1b** has not been previously reported.

(3) (a) Wang, W.; Snieckus, V. *J. Org. Chem.* **1992**, *57*, 424−426. (b) Fu, J.-M.; Zhao, B.-P.; Sharp, M. J.; Snieckus, V. *Can. J. Chem.* **1994**, *72*, 227−236.

(4) Biphenyl carboxylic acids with ether substituents in the 2′ position have been reported to give dibenzopyrans when treated with TFAA and oxalyl chloride.[2]

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(7) (a) The published procedure of Sargent (ref 2) was modified (see the Experimental Section). (b) Dodd, J. H.; Guan, J.; Schwender C. F. *Synth. Commun.* **1993**, *23*, 1003−1008.

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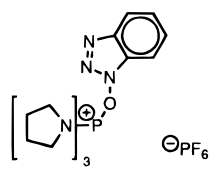
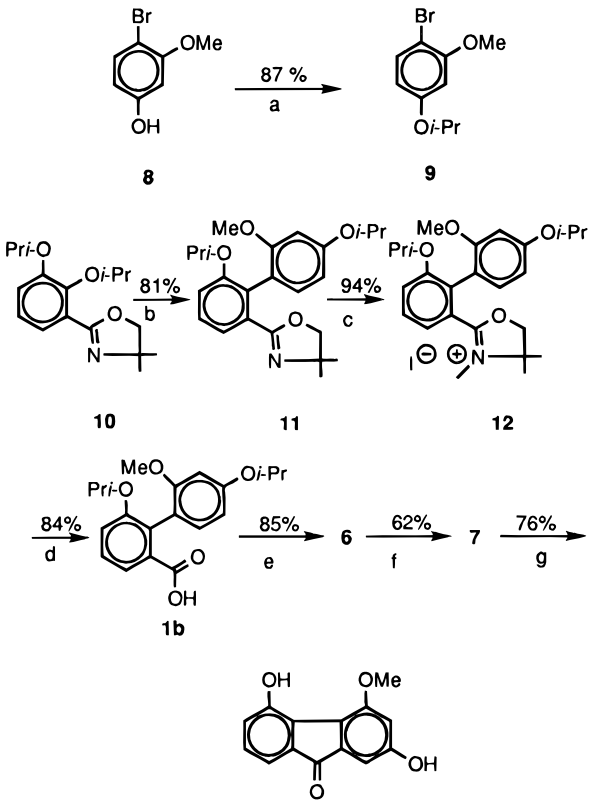
(9) PyBOP has the structure shown below and can be purchased from Nova Biochem, San Diego, CA.



(10) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923−2925.

S0022-3263(96)00136-3 CCC: $12.00

Scheme 2[a]



[a] (a) K_2CO_3, *i*-PrI, 2-butanone; (b) Mg, THF, **9**, 50 °C; (c) MeI, DMSO, rt, 20 h; (d) (1) 20% NaOH, MeOH, Δ; (2) 12 M HCl; (e) PyBOP, CH_2Cl_2, Et_2NH, DIEA; (f) 4.1 equiv of LDA, THF, −50 °C to rt, 48 h; (g) BCl_3, CH_2Cl_2, 0 °C to rt.

(17.52 g, 0.196 mol) in dry THF (200 mL). The mixture was stirred at ambient temperature for 1 h. To this solution was added methyl 2,3-diisopropoxybenzoate[2] (24.82 g, 0.098 mol) dissolved in THF (50 mL). The mixture was stirred overnight under argon, quenched with H_2O (4 mL), and concentrated by evaporation of solvent. The residue was dissolved in CH_2Cl_2, extracted with H_2O, washed with brine, and dried over $MgSO_4$. Filtration and evaporation of solvent gave 33.3 g of a yellow liquid. To this crude product dissolved in CH_2Cl_2 (30 mL) was added dropwise $SOCl_2$ (19 mL, 0.37 mol) at 0−5 °C. Following the addition the reaction mixture was allowed to warm to ambient temperature and stirred for 1.5 h. The mixture was diluted with EtOAc (300 mL) and poured into ice water (500 mL), and the aqueous layer was separated and neutralized with solid K_2CO_3 to pH 9, and then the oily precipitate was extracted into EtOAc. The EtOAc was washed with brine, dried with $MgSO_4$, and filtered. The solvent was evaporated, and final traces of solvent were removed under high vacuum to give **10**[2] as a yellow liquid: 23.6 g (83%) overall; ^{1}H NMR ($CDCl_3$) δ 7.29−7.27 (1H, m), 6.99−6.98 (2H, m), 4.55 (1H, sept, J = 6.1 Hz), 4.44 (1H, sept, J = 6.1 Hz), 4.09 (2H, s), 1.38 (6H, s), 1.31 (3H, d, J = 6.1 Hz), 1.27 (6H, d, J = 6.1 Hz).

4,5-Dihydro-2-[2′-methoxy-4′,6-bis(1-methylethoxy)[1,1′-biphenyl]-2-yl]-4,4-dimethyloxazole (11). To a stirred suspension of Mg (0.917 g, 37.7 mmol), a crystal of I_2, and 3 drops of ethylene dibromide was added dropwise 10 mL of a solution of **9** (8.51 g, 34.7 mmol) dissolved in THF (30 mL). The mixture was warmed to 40 °C, and the remainder of the solution of **9** was added. After the reaction moderated, the mixture was heated at 50 °C for 40 min. To this solution was added oxazoline **10**[2] (11.27 g, 38.0 mmol) in THF (30 mL) dropwise at ambient temperature. The reaction mixture warmed 10 °C during the addition. The reaction mixture was heated and stirred at 50 °C overnight. The mixture was chilled in an ice bath and quenched with saturated NH_4Cl. The THF layer was washed with brine, dried over $MgSO_4$, and filtered. The solvent was evaporated, and the residue was purified by flash chromatography (40% EtOAc/hexane) to give **11** as a pale yellow oil: 11.34 g (81%); ^{1}H NMR ($CDCl_3$) δ 7.32 (1H, dd, J = 7.8, 1.3 Hz), 7.28 (1H, dd, J = 8.0, 7.8 Hz), 7.02 (1H, dd, J = 8.0, 1.2 Hz), 7.00 (d, 1H J = 8.8, 2.4 Hz), 6.47 (1H, dd, J = 7.0, 2.3 Hz), 6.46 (1H, d, J = 2.4 Hz), 4.58 (1H, sept, J = 6.1 Hz), 4.29 (1H, sept, J = 6.2 Hz), 3.74 (1H, d, J = 8.0 Hz), 3.69 (3H, s), 3.62 (1H, d, J = 8.1 Hz), 1.36−1.35 (6H, m), 1.19−1.18 (6H, m), 1.12−1.11 (6H, m);[11] ^{13}C NMR ($CDCl_3$) δ 163.6, 158.2, 155.9, 131.2, 131.0, 129.3, 127.7, 122.1, 119.0, 117.6, 105.7, 110.1, 79.3, 71.5, 69.9, 67.0, 55.4, 28.0, 22.1, 22.0, 21.9. Anal. Calcd for $C_{24}H_{31}NO_4$: C, 72.52; H, 7.86; N, 3.52. Found: C, 72.82; H, 8.07; N, 3.52.

4,5-Dihydro-2-[2′-methoxy-4′,6-bis(1-methylethoxy)[1,1′-biphenyl]-2-yl]-3,4,4-trimethyloxazolium Iodide (12). To a stirred solution of **11** (5.80 g, 14.6 mmol) in dry DMSO[12] (30 mL) was added MeI (12.42 g, 87.5 mmol) at ambient temperature. The resulting mixture was stirred overnight and diluted with dry Et_2O. The precipitate was removed by filtration. The solid was triturated with $CHCl_3$ (400 mL) and filtered. Evaporation of the filtrate followed by recrystallization from MeOH/EtOAc gave **12** as a white solid: 7.40 g (94%); mp 213−214 °C; ^{1}H NMR ($CDCl_3$) δ 7.8 (1H, dd, J = 8.0, 1.1 Hz), 7.47 (1H, dd, J = 8.0, 8.0 Hz), 7.18 (1H, br d, J = 8.2 Hz), 6.94 (1H, d, J = 8.4 Hz), 6.52 (1H, dd, J = 8.4, 2.3 Hz), 6.47 (1H, d, J = 2.3 Hz), 5.09 (1H, d, J = 9.5 Hz), 4.85 (1H, d, J = 9.4 Hz), 4.57 (1H, sept, J = 6.2 Hz), 4.44 (1H, sept, J = 6.0 Hz), 3.68 (3H, s), 2.87 (3H, s), 1.63 (3H, s), 1.33−1.31 (6H, m), 1.28 (3H, s), 1.16−1.15 (6H, m);[11] ^{13}C ($CDCl_3$) δ 172.8, 159.8, 157.6, 155.9, 131.9, 128.1, 122.5, 122.4, 120.5, 118.9, 114.9, 106.4, 100.5, 82.3, 71.2, 70.0, 67.57, 55.7, 30.36, 24.2, 23.4, 21.9, 21.8, 21.7, 21.6. Anal. Calcd for $C_{25}H_{34}NO_4$: C, 55.66; H, 6.35; N, 2.60. Found: C, 55.82; H, 6.42; N, 2.55.

2′-Methoxy-4′,6-bis(1-methylethoxy)[1,1′-biphenyl]-2-carboxylic Acid (1b). Compound **12** (13.2 g, 24.5 mmol) was heated and stirred under reflux overnight in a mixture of 20% aqueous NaOH /MeOH (1/1, 280 mL). The reaction was evaporated until turbid and diluted with H_2O (300 mL). The solution was acidified with concentrated HCl, and the precipitated acid was extracted into CH_2Cl_2. Evaporation of the solvent gave a glass. Crystallization of the glass from cyclohexane gave **1b** as a white solid: 7.10 g (84%); mp 118−120 °C; IR (KBr) 1697 (C=O), 1674 (C=O); ^{1}H NMR ($CDCl_3$) δ 7.52 (1H, dd, J = 7.7, 1.2 Hz), 7.30 (1H, dd, J = 8.0, 8.0 Hz), 7.13 (1H, dd, J = 8.3, 1.2 Hz), 7.06 (1H, d, J = 8.3 Hz), 6.56 (1H, dd, J = 8.4, 2.4 Hz), 6.46 (1H, J = 2.3 Hz), 4.59 (1H, sept, J = 6.1 Hz), 4.26 (1H, sept, J = 6.3 Hz), 3.66 (3H, s), 1.37 (6H, J = 6.2 Hz), 1.15 (3H, d, J = 6.1 Hz), 1.08 (3H, d, J = 6.0 Hz); ^{13}C NMR ($CDCl_3$) δ 171.8, 158.7, 157.7, 156.1, 132.4, 131.6, 129.6, 127.8, 122.6, 119.9, 117.4, 105.9, 100.2, 71.9, 69.9, 55.3, 22.2, 22.1, 21.9, 21.9. Anal. Calcd for $C_{20}H_{24}O_5$: C, 69.75; H, 7.02. Found: C, 69.83; H, 6.90.

***N*,*N*-Diethyl-2′-methoxy-4′,6-bis(1-methylethoxy)[1,1′-biphenyl]-2-carboxamide (6).** To a mixture of **1b** (3.40 g, 9.9 mmol), PyBOP[9] (5.15 g, 9.9 mmol), and Et_2NH (0.88 g, 12.1 mmol) in CH_2Cl_2 (30 mL) was added *N*,*N*-diisopropylethylamine (2.82 g, 21.8 mmol). The resulting mixture was stirred overnight under argon. The solvent was evaporated, and the residue was dissolved in EtOAc (250 mL). The EtOAc solution was extracted with 5% HCl (3 × 70 mL), washed with brine, extracted with $NaHCO_3$ (3 × 70 mL), and dried over $MgSO_4$. Filtration and evaporation of solvent gave a light brown oil. The oil was purified by flash chromatography (40% EtOAc/hexane), affording the desired amide as a solid. The solid was recrystallized from hexane (50 mL), giving **6** as a white solid: 3.35 g (85%); mp 73−74 °C; IR (neat) 1629 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$) δ 7.28 (1H, dd, J = 8.0, 8.0 Hz), 7.15 (1H, d, J = 8.2 Hz), 6.92 (1H, d, J = 8.0 Hz), 6.92 (1H, d, J = 8.0 Hz), 6.46 (1H, dd, J = 8.2, 2.3 Hz), 6.43 (1H, d, J = 2.1 Hz), 4.55 (1H, sept, J = 6.1 Hz), 4.32 (1H, sept, J = 6.1 Hz), 3.77 (1H, m), 3.68 (3H, s), 3.19 (1H, m), 2.76 (1H, m), 2.63 (1H, m), 1.3−1.31 (6H, m), 1.18 (3H, d, J = 6.1 Hz), 1.09 (3H, d, J = 6.0 Hz), 0.84 (3H, t, J = 7.1 Hz), 0.67 (3H, t, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$) δ 170.0, 158.5, 156.0, 139.4, 132.3, 128.4, 126.0, 118.2, 117.5, 114.7, 105.5, 100.0, 71.1, 69.8, 55.1, 41.6, 37.6, 22.2, 22.1, 21.9, 21.7, 13.7, 11.8. Anal. Calcd

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(12) Meyers, A. I.; Slade, J. *J. Org. Chem.* **1980**, *45*, 2785−2791.

for $C_{24}H_{33}NO_4$: C, 72.15; H, 8.33; N, 3.51. Found: C, 72.20; H, 8.56; N, 3.56.

4-Methoxy-2,5-bis(1-methylethoxy)-9*H*-fluoren-9-one (7). To a stirred solution of LDA (15.0 mmol) in THF (30 mL) was added **6** (1.28 g, 3.2 mmol) in THF (15.0 mL) at −50 °C. The resulting yellow solution was allowed to warm to ambient temperature and stirred for 48 h under argon. During this period the solution turned a brilliant red color. The red solution was quenched with saturated NH_4Cl (30 mL). The mixture was diluted with THF (150 mL) and separated. The NH_4Cl layer was extracted with THF (50 mL), and the combined organic extracts were dried over $MgSO_4$. The THF was evaporated and the resulting red oil purified by flash chromatography (15% EtOAc/hexane), affording a red solid. Recrystallization from hexane afforded **7** as red flakes: 0.65 g (62%); mp 74−75 °C; IR (KBr) 1712 cm^{-1} (C=O); UV (MeOH) $\lambda_{max} = 476$ nm, $\epsilon = 1570$, $\lambda_{max} = 339$ nm, $\epsilon = 3489$, $\lambda_{max} = 276$, $\epsilon = 40\ 200$; ^1H NMR ($CDCl_3$) δ 7.27 (1H, dd, $J = 6.9$ Hz, $J = 1.2$ Hz), 7.1 (1H, dd, $J = 8.3$, 6.8 Hz), 7.04 (1H, dd, $J = 8.2$, 1.2 Hz), 6.86 (1H, d, $J = 2.2$ Hz), 6.57 (1H, d, $J = 2.2$ Hz), 4.59 (1H, m), 3.88 (3H, s), 1.38 (6H, d, $J = 6.1$ Hz), 1.35 (6H, d, $J = 6.1$ Hz). Anal. Calcd for $C_{20}H_{22}O_4$: C, 73.60; H, 6.79. Found: C, 73.46; H, 6.83.

2,5-Dihydroxy-4-methoxy-9*H*-fluoren-9-one (Dengibsin, 13). To a stirred solution of **7** (0.58 g, 1.8 mmol) in CH_2Cl_2 (15.0 mL) was added BCl_3 (7.2 mL, 7.2 mmol) (1.0 M) at 0 °C. The green mixture was allowed to warm to ambient temperature and stirred for 2 h under argon. The mixture was cooled to 0 °C and quenched with H_2O (20 mL). The precipitated red solid was removed by filtration and recrystallized from MeOH/H_2O, affording 0.331 g (76%)[13] of **13** as a red solid: mp 235−237 °C (lit,[2] mp 238−240 °C); IR (KBr) 1697, 1614, 1597 cm^{-1}; UV (EtOH) $\lambda_{max} = 265$, 274, and 338 nm ($\epsilon = 32\ 576$, 36 000, and 3406 nm); ^1H NMR (CD_3COCD_3) δ 9.22 (1H, broad s), 9.92 (1H, s), 7.16−7.09 (2H, m), 6.96 (1H, dd, $J = 7.02$, 2.1 Hz), 6.81 (1H, d, $J = 2.0$ Hz), 6.78 (1H, d, $J = 2.1$ Hz). Anal. Calcd for $C_{14}H_{10}O_4$: C, 69.42; H, 4.16. Found: C, 69.03; H, 4.26.

Acknowledgment. The authors wish to acknowledge Drs. V. Snieckus, Jim Fu, Braulio Santiago, and Alan Warshawsky for helpful discussions. The authors also wish to acknowledge Drs. Dirk Friedrich and Ed Huber for the NMR data and interpretations.

JO9601369

(13) In a later experiment, 2.03 g of **7** was converted into 1.40 g of dengibsin **13**.