Efficient, Highly Enantioselective Synthesis of Selina-1,3,7(11)-trien-8-one, a Major Component of the Essential Oil of *Eugenia uniflora*

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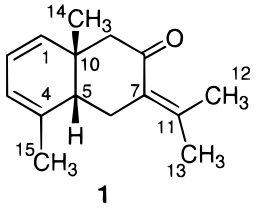
Received February 9, 2000

The first synthesis of selina-1,3,7(11)-trien-8-one (**1**), a major constituent of the essential oil from the leaves of *Eugenia uniflora*, has been accomplished, with excellent stereo- and regiocontrol, in eight steps and in 12% overall yield from the known octalone derivative **2a**.

Eugenia uniflora L. (Myrtaceae) is a shrubby tree indigenous to Brazil, but now found through exportation in India, China, Sri Lanka, Egypt, Nigeria, and other tropical and subtropical regions.[1−3] The essential oil derived from this plant has been used in folk medicine to treat digestive disorders,[4] while tea from the leaves has been employed against fever and rheumatism;[5] wine from the cherry-like fruit also has been reported to possess medicinial properties.[6] Recently, it has been found that the essential oil obtained from the leaves of *E. uniflora* exhibits antimicrobial activity against the Gram-positive bacteria *Sarcina luteu* and *Mycobacterium phlei* and antifungal activity against *Candida albicans* and *Trichophyton mentagrophytes*.[2]

In 1988, Weyerstahl and co-workers[1] isolated a major constituent (17%) from the oxygenated sesquiterpene-rich essential oil of Nigerian *E. uniflora* to which they assigned by NMR the structure and relative stereochemistry shown in **1**. This new selinatrienone has since been found as the major component in *E. uniflora* essential oil of Egyptian[2] and Brazilian[3] origins (20.3 and 48.5%, respectively). We report herein an efficient, enantioselective approach to (−)-selina-1,3,7(11)-trien-8-one (**1**) that establishes the structure and relative stereochemistry of the natural product.[7]



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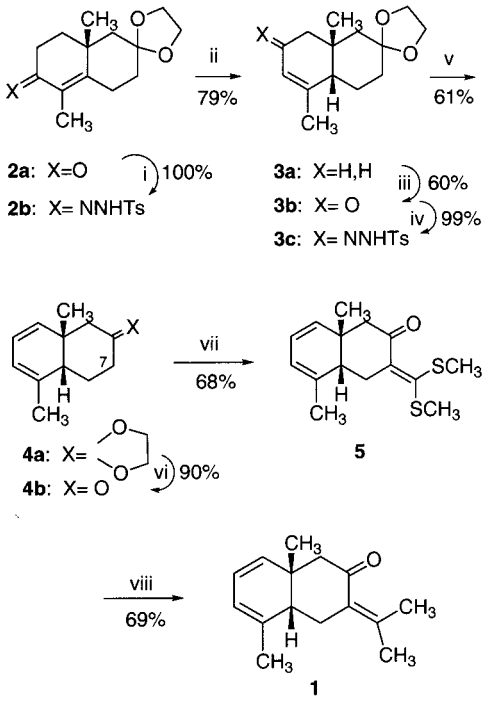
Dextrorotatory octalone **2a** (Scheme 1), of known[8] absolute stereochemistry, was readily secured as previously described[8,9] and then recrystallized to afford highly enantioenriched starting material (≥98% enantiomer excess). This enone was next converted in quantitative yield into its tosylhydrazone derivative **2b**, which underwent double-bond translocation with concomitant carbonyl reduction under the "alkene walk" procedure[10] to give, in a highly stereoselective manner, the desired cis-fused octalone derivative **3a** (79% yield). Only 3% of the isomeric trans product[8b,11] was generated in this transformation.

Among the various possibilities examined for the introduction of the remaining double bond, the most effective in terms of yield and regioselectivity proved to be that based on a second tosylhydrazone transformation, the Shapiro reaction.[12] Toward this end, the octalone derivative **3a** was allylically oxidized with the Corey modified[13] Collins' reagent to provide enone **3b** (60%), which was then converted into its tosylhydrazone **3c** in essentially quantitative yield. Under carefully optimized conditions, **3c** was decomposed with methyllithium in THF to produce the hexalone derivative **4a** (61%) with no detectable formation of any isomeric diene.

Mild acid treatment of this acetal engendered keto diene **4b** (90%), which was converted, albeit in only 10% yield, into **1** through sequential treatment of the C-7 methoxycarbonyl derivative with sodium hydride, methyllithium, and *p*-toluenesulfonic acid.[14] A more satisfactory procedure involved the use of ketene dithioacetal **5**, easily prepared in 68% yield from keto diene **4b** by treatment with

Scheme 1[a]



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[a]Key: i, $TsNHNH_2$, THF, Δ. ii, Catecholborane, $CHCl_3$, 0 °C; CH_3CO_2Na, 65 °C. iii, CrO_3·DMP, CH_2Cl_2, 0 → 20 °C. iv, $TsNHNH_2$, THF, Δ. v, CH_3Li, THF, 0 → 20 °C. vi, CH_3CO_2H–H_2O, 100 °C. vii, LHMDS, THF–HMPA, -78 °C; CS_2, -78 → 0 °C; LHMDS, -78 °C; CH_3I, -78 → 20 °C. viii, $LiCu(CH_3)_2$, $(C_2H_5)_2O$, -78 °C.

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10.1021/np000065f CCC: $19.00
Published on Web 08/02/2000

lithium hexamethyldisilazane (LHMDS), carbon disulfide, and methyl iodide.[15] In the presence of ethereal methyllithium, **5** experienced clean double addition−elimination[15] to produce (−)-selina-1,3,7(11)-trien-8-one (**1**) (69%), whose ^{1}H and ^{13}C NMR spectra were in excellent agreement with those of natural **1**.

Thus, the first synthesis of this novel selinatrienone has been accomplished with high stereo- and regiocontrol, in eight steps and in 12% overall yield from octalone **2a**. The synthesis, although indicating only probable absolute stereochemistry,[16] fully confirms the structure and relative stereochemistry previously proposed for the natural product.

Experimental Section

General Experimental Procedures. Thin-layer chromatography was performed on Merck 60F_{254} (0.2 mm) sheets, which were visualized with molybdophosphoric acid in ethanol. Merck 70−230 Si gel 60 was employed for column chromatography. A Nicolet 400 spectrophotometer was used to record IR spectra (neat or as Nujol film). Bruker AC 200 and AV 300 spectrometers were employed for the NMR spectra ($CDCl_3$ solutions, with residual $CHCl_3$ for ^{1}H NMR and $CDCl_3$ for ^{13}C NMR as the references). Optical rotations were measured with a Perkin-Elmer 241 polarimeter. Melting points were taken on a Büchi-Tottoli apparatus and are not corrected. Mass spectra were obtained on an AEI MS-30 mass spectrometer (70 eV, direct insert probe). Microanalyses were performed by the Central Service of the CNRS.

The reaction mixture was generally poured into water, and the separated aqueous phase was then thoroughly extracted with the specified solvent. After being washed with 10% aqueous HCl and/or $NaHCO_3$ (if required), H_2O, and saturated aqueous NaCl, the combined organic phases were dried over anhydrous Na_2SO_4 or $MgSO_4$ and then filtered and concentrated under reduced pressure on a Büchi Rotovapor to yield the crude reaction product. Tetrahydrofuran and ether were distilled from sodium−benzophenone, and $CHCl_3$, CH_2Cl_2, and HMPA were distilled from calcium hydride. All reactions were carried out under an argon atmosphere.

(4′a*R*,8′a*R*)-5′,8′a-Dimethyl-3′,4′,4′a,7′,8′,8′a-hexahydro-1′*H*-spiro([1,3]dioxolane-2,2′-naphthalene) (3a). To a solution of octalone **2a**[8,9] (73 mg, 0.31 mmol) in dry THF (1.1 mL) was added tosylhydrazide (97 mg, 0.52 mmol), and the reaction mixture was stirred under reflux for 3.5 h. The solvent was then removed under reduced pressure, and the residue was purified by Si gel chromatography with 30% ethyl acetate in pentane to give 125 mg (100%) of tosylhydrazone **2b** as a white amorphous solid: mp 95−98 °C (dec); $[\alpha]^{20}_D$ +127° (*c* 0.94, $CHCl_3$); IR ν_{max} 3423, 3225, 1706, 1653, 1600, 1340, 1174, 1095, 1037 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.56 (4H, AB, δ_a = 7.85, δ_b = 7.27, J_{ab} = 8.2 Hz), 7.58−7.22 (1H, br s), 4.02−3.81 (4H, m), 2.70 (1H, dt, J = 15.6, 4.0 Hz), 2.40 (3H, s), 2.57−1.85 (3H, m), 1.78 (3H, s), 1.75−1.17 (6H, m), 1.12 (3H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 155.1, 147.8, 143.6, 135.2, 129.2 (2×), 128.0 (2×), 124.8, 108.0, 64.4, 63.4, 48.0, 36.5, 35.6, 34.5, 24.6, 23.6, 21.4, 20.4, 12.4; CIMS *m*/*z* 405 (40), 251 (100), 236 (60), 221 (8), 189 (19), 174 (7.3); HREIMS *m*/*z* 404.1771 (calcd for $C_{21}H_{28}N_2O_4S$, 404.1770).

Catecholborane (0.500 mL, 0.562 g, 4.69 mmol) was added to a solution of tosylhydrazone **2b** (1.06 g, 2.62 mmol) in freshly distilled $CHCl_3$ (26 mL) at 0 °C, and the reaction mixture was stirred at 0 °C for 0.5 h. Sodium acetate trihydrate (4.34 g, 31.9 mmol) was then added, and the mixture was heated at 65 °C for 0.75 h. After being cooled to 20 °C, the mixture was treated with saturated aqueous $NaHCO_3$ solution, and the product was isolated with ether in the usual way (see general experimental procedures) and purified by Si gel chromatography with 20% ethyl acetate in pentane to yield 0.460 g (79%) of olefin **3a**: $[\alpha]^{20}_D$ −27° (*c* 0.88, $CHCl_3$); IR ν_{max} 3040, 1448, 1356, 1113, 1091 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 5.26 (1H, br s), 4.22−3.80 (4H, m), 2.04−1.77 (4H, m), 1.72−1.55 (5H, m), 1.52−1.30 (4H, m), 1.07−0.95 (1H, m), 0.89 (3H, s); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 135.3, 120.1, 109.1, 64.2, 63.5, 46.0, 45.9, 34.0, 33.5, 28.7, 27.2, 26.0, 23.0, 22.5; CIMS *m*/*z* 223 (100), 161 (6), 126 (6.5), 108 (8), 99 (36); HREIMS *m*/*z* 222.1622 (calcd for $C_{14}H_{22}O_2$, 222.1620).

(4′a*R*,8′a*R*)-5′,8′a-Dimethyl-4′,4′a,8′,8′a-tetrahydro-1′*H*,3′*H*-spiro([1,3]dioxolane-2,2′-naphthalen)-7′-one (3b). To a suspension of chromic anhydride (800 mg, 8.00 mmol) in CH_2Cl_2 (5.0 mL) at 0 °C was added 3,5-dimethylpyrazole (DMP) (650 mg, 6.76 mmol). After being stirred for 0.5 h at 20 °C, the reaction mixture was cooled to 0 °C, and a solution of olefin **3a** (95 mg, 0.43 mmol) in CH_2Cl_2 (3.0 mL) was added. After being stirred for an additional 1 h at 20 °C, the mixture was poured into pentane−ether (1:1). The resulting mixture was filtered through Celite, the filtrate concentrated under reduced pressure and the residue purified by column chromatography on Si gel (pretreated with 2.5% v/v of triethylamine) with 30% ethyl acetate in cyclohexane to afford 61 mg (60%) of enone **3b**:[17] mp 70 °C; $[\alpha]^{20}_D$ −32.6° (*c* 1.0, $CHCl_3$); IR ν_{max} 1668, 1640, 1440, 1364, 1265, 1106, 1053, 954 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.76 (1H, s), 3.94−3.82 (4H, m), 2.50 (2H, AB, δ_a = 3.16, δ_b = 1.84, J_{ab} = 17.3 Hz), 1.92 (3H, d, J = 1.4 Hz), 1.90−1.68 (3H, m), 1.64−1.44 (4H, m), 0.95 (3H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 200.0, 163.2, 125.0, 108.1, 64.4, 63.6, 48.4, 45.7, 44.3, 37.1, 34.7, 28.5, 26.2, 23.3; CIMS *m*/*z* 237 (100), 135 (27), 99 (39); *anal.* C 71.21%, H 8.59%, calcd for $C_{14}H_{20}O_3$, C 71.16%, H 8.53%.

(4′a*R*,8′a*S*)-5′,8′a-Dimethyl-3′,4′,4′a,8′a-tetrahydro-1′*H*-spiro([1,3]dioxolane-2,2′-naphthalene) (4a). Tosylhydrazide (66 mg, 0.35 mmol) was added to a solution of enone **3b** (50 mg, 0.21 mmol) in THF (0.80 mL), and the mixture was refluxed for 4 h. Additional tosylhydrazide (30 mg, 0.16 mmol) was added, and reflux was continued for 1.75 h. The solvent was then removed under reduced pressure, and the crude mixture was chromatographed on Si gel with 30% ethyl acetate in cyclohexane to give 85 mg (99%) of tosylhydrazone **3c** (ca. 4:1 mixture of isomers) as a white solid: mp 118 °C (dec); $[\alpha]^{20}_D$ −42.1° (*c* 1.0, $CHCl_3$); IR ν_{max} 3210, 1638, 1600, 1448, 1402, 1326 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz, major isomer) δ 7.54 (4H, AB, δ_a = 7.82, δ_b = 7.26, J_{ab} = 8.2 Hz), 5.83 (1H, s), 3.95−3.75 (4H, m), 2.81 (1H, d, J = 17.0 Hz), 2.38 (3H, s), 1.78 (3H, s), 1.95−1.35 (6H, m), 1.35−1.10 (3H, m), 0.85 (3H, s); ^{13}C NMR ($CDCl_3$, 75 MHz, major isomer) δ 155.4, 148.1, 143.7, 135.6, 129.4, 127.9, 121.2, 108.2, 64.5, 63.6, 47.8, 45.7, 34.9, 30.7, 29.0, 26.8, 26.1, 22.8, 21.5; CIMS *m*/*z* 405 (100), 303 (9), 251 (21), 236 (30), 221 (19), 189 (19); *anal.* C 62.49%, H 7.09%, N 6.55%, calcd for $C_{21}H_{28}N_2O_4S$, C 62.35%, H 6.98%, N 6.93%.

To a solution of tosylhydrazone **3c** (500 mg, 1.24 mmol) in THF (35 mL) at 0 °C was added a 1.6 M solution of methyllithium (3.5 mL, 5.6 mmol) in ether. The reaction mixture was stirred for 1.5 h at 0 °C and 1 h at 20 °C, after which it was processed with ethyl acetate in the usual way (see general experimental procedures) and the crude product was purified by Si gel chromatography with 30% ethyl acetate in cyclohexane to afford 166 mg (61%) of diene **4a**: $[\alpha]^{20}_D$ −240° (*c* 0.8, $CHCl_3$); IR ν_{max} 3035, 1650, 1585, 1448, 1356, 1326, 1258, 1106, 1053 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.72 (1H, dd, J = 9.3, 5.2 Hz, H-2), 5.57−5.49 (1H, m, H-3), 5.28 (1H, d, J = 9.3 Hz, H-1), 4.01−3.83 (4H, m, OCH_2CH_2O), 1.77 (3H, s, H-15), 1.80−1.37 (7H, m, H-5, H-6, H-7, H-9), 0.91 (3H, s, H-14); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 138.3 (C-4), 133.7 (C-1), 121.1 (C-3), 116.9 (C-2), 108.7 (C-8), 64.6 (OCH_2), 63.7 (OCH_2), 46.7 (C-5), 45.6 (C-9), 36.8 (C-10), 34.7 (C-7), 26.8 (C-14), 24.0 (C-6), 22.3 (C-15); CIMS *m*/*z* 221(100), 171 (40), 158 (12), 126 (21); HRFABMS *m*/*z* 220.1480 (calcd for $C_{14}H_{20}O_2$, 220.1463).

(4a*R*,8a*S*)-5,8a-Dimethyl-3,4,4a,8a-tetrahydro-1*H*-naphthalen-2-one (4b). A solution of diene **4a** (250 mg, 1.13 mmol) in 85% acetic acid (8.5 mL) was heated at 100 °C for 0.5 h. The solvent was removed under reduced pressure, and the product was processed with ether in the normal manner (see general experimental procedures) and then filtered rapidly through a short Si gel column to afford 181 mg (90%) of keto diene **4b**: $[\alpha]^{20}_D$ −197° (*c* 0.8, $CHCl_3$); IR ν_{max} 3028, 1718, 1645, 1584, 1443, 1363, 1299, 1238 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.76 (1H, dd, J = 9.3, 5.2 Hz), 5.64−5.54 (1H, m), 5.26 (1H, d, J = 9.3 Hz), 2.33−2.18 (4H, m), 2.05−1.93 (2H, m), 1.80

(3H, s), 1.72−1.53 (1H, m), 0.99 (3H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 210.6, 139.0, 130.8, 123.6, 117.7, 52.2, 45.9, 41.1, 40.9, 26.5, 26.4, 22.2; CIMS *m*/*z* 194 (46), 177 (38), 159 (11), 119 (100), 105 (5); HREIMS *m*/*z* 176.1203 (calcd for $C_{12}H_{16}O$, 176.1201).

(4a*R*,8a*S*)-(Bis-methylsulfanyl-methylene)-dimethyl-3,4,4a,8a-tetrahydro-1*H*-naphthalen-2-one (5). To a stirred solution of keto diene **4b** (48.5 mg, 0.28 mmol) in THF (1.00 mL) and HMPA (0.050 mL) at −78 °C was added a 1.0 M solution of LHMDS in THF (0.30 mL, 0.30 mmol) and, after 0.5 h, carbon disulfide (0.020 mL, 25 mg, 0.33 mmol). The reaction mixture was allowed to warm to 0 °C over 2 h, and then cooled to −78 °C and treated with an additional 0.30 mL (0.30 mmol) of the 1.0 M LHMDS solution. After being stirred at −78 °C for 0.5 h, the solution was treated with methyl iodide (0.090 mL, 205 mg, 1.44 mmol), allowed to warm to 20 °C over 1 h, and then stirred at this temperature for 1 h. The crude product was isolated with ether in the usual manner (see general experimental procedures) and purified by Si gel chromatography with 10% ether in pentane to afford 52.5 mg (68%) of dithioacetal **5**: $[\alpha]^{20}_D$ −197° (*c* 1.1, $CHCl_3$); IR ν_{max} 3026, 1691, 1669, 1500, 1433, 1249 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.74 (1H, dd, J = 9.4, 5.3 Hz), 5.64−5.59 (1H, m), 5.30 (1H, d, J = 9.4 Hz), 2.85 (2H, AB of ABX, δ_a = 3.18, δ_b = 2.53, J_{ab} = 15.2 Hz, J_{ax} = 4.9 Hz, J_{bx} = 10.4 Hz), 2.43 (2H, AB, δ_a = 2.57, δ_b = 2.28, J_{ab} = 14.7 Hz), 2.31 (6H, s), 2.10−1.97 (1H, X of ABX, J_{ax} = 4.9 Hz, J_{bx} = 10.4 Hz), 1.84 (3H, s), 1.03 (3H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 199.7, 143.0, 140.0, 137.8, 131.5, 123.1, 118.1, 52.7, 46.3, 38.4, 33.3, 26.6, 22.2, 18.0 (2×); CIMS *m*/*z* 281 (100), 175 (19), 159 (17); HRFABMS *m*/*z* 280.0961 (calcd for $C_{15}H_{20}OS_2$, 280.0956).

(4a*R*,8a*S*)-3-Isopropylidene-5,8a-dimethyl-3,4,4a,8a-tetrahydro-1*H*-naphthalen-2-one (1). To a stirred suspension of copper iodide (40 mg, 0.21 mmol) in anhydrous ether (1.5 mL) at 0 °C was added a 1.6 M solution of methyllithium in ether (0.26 mL, 0.42 mmol). The solution was cooled to −78 °C, and treated dropwise with a solution of dithioacetal **5** (30 mg, 0.11 mmol) in ether (1.5 mL). The reaction mixture was stirred for 0.5 h at −78 °C and then quenched with CH_3OH. The reaction mixture was then processed with ether in the normal manner (see general experimental procedures), and the crude product was purified by Si gel column chromatography with 10% ether in pentane to yield 16 mg (69%) of **1**: $[\alpha]^{20}_D$ −258° (*c* 1.0, $CHCl_3$); IR ν_{max} 3026, 1687, 1620, 1444, 1373, 1293, 1266 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.75 (1H, dd, J = 9.5, 4.8 Hz, H-2), 5.64−5.58 (1H, m, H-3), 5.30 (1H, d, J = 9.5 Hz, H-1), 2.45 (2H, AB of ABX, δ_a = 2.63, δ_b = 2.26, J_{ab} = 15.0 Hz, J_{ax} = 4.5 Hz, J_{bx} = 10.1 Hz, H-6), 2.36 (2H, AB, δ_a = 2.45, δ_b = 2.28, J_{ab} = 14.6 Hz, H-9), 1.98 (1H, X of ABX, J_{ax} = 4.5 Hz, J_{bx} = 10.1 Hz, H-5), 1.92 (3H, d, J = 1.8 Hz, H-12 or H-13), 1.83 (3H, s, H-15), 1.76 (3H, d, J = 1.0 Hz, H-12 or H-13), 1.02 (3H, s, H-14); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 203.8 (C-8), 139.5 (C-11), 138.3 (C-4), 132.6 (C-7), 131.7 (C-1), 123.0 (C-3), 118.0 (C-2), 53.4 (C-9), 46.1 (C-5), 38.4 (C-10), 29.8 (C-6), 26.7 (C-14), 22.6 (C-15), 22.2 (C-12 or C-13), 21.7 (C-12 or C-13); EIMS *m*/*z* 216 (5), 149 (10), 110 (19), 97 (30), 69 (29), 57 (78), 43 (100); HREIMS *m*/*z* 216.1514 (calcd for $C_{15}H_{20}O$, 216.1514).

Acknowledgment. We thank Prof. Y. Yallée, Prof. E. Barreiro, and Dr. E. Muri for their interest in our work and Prof. P. Weyerstahl and Prof. H. Marschall-Weyerstahl for spectra and useful information. In addition, Prof. A. A. Craveiro is thanked for a helpful exchange. A fellowship award from MRES to A.P. and financial support from the CNRS (UMR 5616) and the Université Joseph Fourier are gratefully acknowledged.

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(16) The reported[1] optical rotation of the natural material is considerably different from that of our synthetic substance (−6 vs. −258°). This may be due to the small amount of the natural material that was available and/or the questionable polarimeter readings at the time of the isolation (private communication, P. Weyerstahl).
(17) HPLC (Chiracel OD-H, 5 μm, hexane−2-propanol (7:3), 0.5 cm^3/min, t_R 11.32 min (versus 12.90 min)) indicated an enantiomeric excess for enone **3b** of ≥98%.

NP000065F