# Concise Synthesis of *cis*- and *trans*-Theaspirones via Oxonium Ion-Initiated Pinacol Ring Expansion

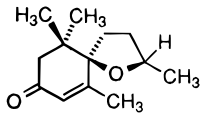
Leo A. Paquette,* James C. Lanter,[1] and Hui-Ling Wang[2]

*Evans Chemical Laboratories, The Ohio State University, Columbus, Ohio 43210*

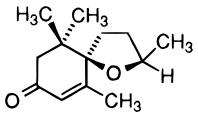
*Received October 23, 1995*[⊗]

The odoriferous principle of black tea has been produced from 2,2-dimethylcyclopentanone. The reaction sequence begins with 1,2-addition of 5-lithio-2-methyl-2,3-dihydrofuran to this ketone and immediate acid-catalyzed ring expansion of the resulting carbinols to a separable pair of spiro ethers. Individual conversion of these diastereomers to α,β-unsaturated ketones is followed by tandem condensation with the methyllithium−lithium bromide complex and oxidation with pyridinium chlorochromate.

A thrust to identify the centrally important aroma constituent of black tea was rewarded in 1968 with the isolation of theaspirone by Ina and co-workers.[3] A year later, Nakatani and Hamanishi confirmed the general structural characteristics by synthesis and showed further that only the cis isomer **2** and not the trans epimer **1** possesses a sweet, tealike odor.[4] The absolute configuration of (−)-**2** was subsequently elucidated.[5]



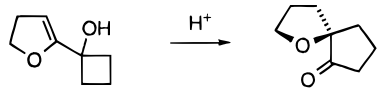
**1**



**2**

Following these developments, a number of syntheses of **1** and/or **2** have been reported. Although there are a few exceptions,[6−8] the great majority of these approaches have utilized α- or β-ionone as starting material.[4,9−14] The present report describes a very different approach to **1** and **2** in racemic form. Featured is an efficient assembly of the spirotetrahydrofuran ring without the disadvantages associated with the previous efforts which have been earlier delineated.[13]

The central reaction involves the actuation of an oxonium ion-induced pinacol rearrangement as exemplified by the conversion of **3** to **4**.[15] This acid-catalyzed isomerization with ring expansion has previously been utilized in the elaboration of unusual ionophoric substances,[16,17] novel spirocyclic glycosides,[18] and sesquiterpenoids such as dactyloxenes-B and -C[19] as well as grindelic acid.[20]



**3** **4**

## Results and Discussion

The convergent step in the synthesis depended on the availability of dihydrofuran **7**. Although this heterocyclic building block has been previously reported,[21] we began by improving the efficiency with which it can be prepared. To this end, γ-valerolactone (**5**) was reduced to the lactol with DIBAL-H and esterified with benzoyl chloride to give **6** in 94% yield (Scheme 1). Simply heating **6** in a Kugelrohr apparatus at 180 °C under reduced pressure gave **7** in a high state of purity.

The metalation of **7** with *tert*-butyllithium and subsequent condensation with 2,2-dimethylcyclopentanone[22] gave the highly reactive alcohols **8** in equivalent amounts.

---

[⊗] Abstract published in *Advance ACS Abstracts,* January 15, 1996.

(1) GANN Fellow, 1993−1995.

(2) On leave from the Department of Chemistry, National Tsing Hua University, Hsinchu 30043, Taiwan, Republic of China.

(3) Ina, K.; Sakato, Y.; Fukami, H. *Tetrahedron Lett.* **1968**, 2777.

(4) Nakatani, Y.; Yamanishi, T. *Tetrahedron Lett.* **1969**, 1995. Rather than coin new nomenclature for **1** and **2**, we have simply adopted the cis/trans notation earlier used to differentiate these isomers.

(5) (a) Ina, K.; Eto, H. *Agr. Biol. Chem.* **1972**, *36*, 1659.b) Weiss, G.; Koreeda, M.; Nakanishi, K. *J. Chem. Soc., Chem. Commun.* **1973**, 565.

(6) Marx, J. N. *Tetrahedron* **1975**, *31*, 1251.

(7) (a) Bäckvall, J.-E.; Andersson, P. G. *J. Org. Chem.* **1991**, *56*, 2274.b) Andersson, P. G.; Nilsson, Y. I. M.; Bäckvall, J.-E. *Tetrahedron* **1994**, *50*, 559.

(8) Weyerstahl, P.; Meisel, T. *Liebigs Ann. Chem.* **1994**, 415.

(9) Heckman, R. A.; Roberts, D. L. *Tetrahedron Lett.* **1969**, 2701.

(10) Ina, K.; Takano, T.; Imai, Y.; Sakato, Y. *Agr. Biol. Chem.* **1972**, *36*, 1033.

(11) Kaiser, R.; Kappeier, A.; Lamparsky, D. *Helv. Chim. Acta* **1978**, *61*, 387.

(12) Mayer, H. *Pure Appl. Chem.* **1979**, *51*, 535.

(13) Könst, W. M. B.; Apeldoorn, W.; Boelens, H. *Synth. Commun.* **1980**, *10*, 899.

(14) Etoh, H.; Ina, K.; Iguchi, M. *Agr. Biol. Chem.* **1980**, *44*, 2871.

(15) (a) Paquette, L. A.; Lawhorn, D. E.; Teleha, C. A. *Heterocycles* **1990**, *30*, 765. (b) Paquette, L. A.; Andrews, J. F. P.; Vanucci, C.; Lawhorn, D. E.; Negri, J. T.; Rogers, R. D. *J. Org. Chem.* **1992**, *57*, 3956.

(16) (a) Negri, J. T.; Rogers, R. D.; Paquette, L. A. *J. Am. Chem. Soc.* **1991**, *113*, 5073. (b) Paquette, L. A.; Negri, J. T.; Rogers, R. D. *J. Org. Chem.* **1992**, *57*, 3947.

(17) (a) Paquette, L. A.; Branan, B. M.; Friedrich, D.; Edmondson, S. D.; Rogers, R. D. *J. Am. Chem. Soc.* **1994**, *116*, 506. (b) Branan, B. M.; Paquette, L. A. *J. Am. Chem. Soc.* **1994**, *116*, 7658. (c) Paquette, L. A.; Branan, B. M. *Heterocycles* **1995**, *40*, 101. (d) Paquette, L. A.; Branan, B. M.; Rogers, R. D. *J. Org. Chem.* **1995**, *60*, 1852. (e) Paquette, L. A.; Branan, B. M.; Rogers, R. D.; Bond, A. H.; Lange, H.; Gleiter, R. *J. Am. Chem. Soc.* **1995**, *117*, 5992.

(18) Paquette, L. A.; Dullweber, U.; Cowgill, L. D. *Tetrahedron Lett.* **1993**, *34*, 8019.

(19) (a) Paquette, L. A.; Lord, M. D.; Negri, J. T. *Tetrahedron Lett.* **1993**, *34*, 5693. (b) Lord, M. D.; Negri, J. T.; Paquette, L. A. *J. Org. Chem.* **1995**, *60*, 191.

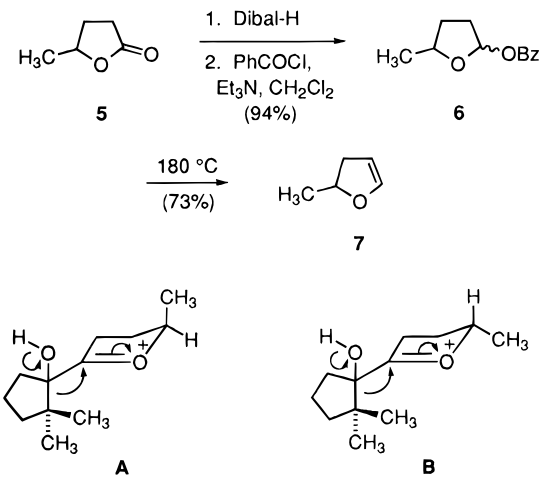
(20) Paquette, L. A.; Wang, H.-L. *Tetrahedron Lett.* **1995**, *36*, 6005.

(21) For preparation of the lactol, consult: (a) Arth, G. E. *J. Am. Chem. Soc.* **1953**, *75*, 2413. (b) Tomooka, K.; Okinaga, T.; Suzuki, K.; Tsuchihashi, G. *Tetrahedron Lett.* **1987**, *28*, 6335. (c) Ishii, Y.; Yoshida, T.; Yamawaki, K.; Ogawa, M. *J. Org. Chem.* **1988**, *53*, 5549. (d) Schmitt, A.; Reissig, H. U. *Synlett* **1990**, 40. (e) Ragoussis, V.; Theodorou, V. *Synthesis* **1993**, 84. (f) Masuyama, Y.; Kobayashi, Y.; Kurusu, Y. *J. Chem. Soc., Chem. Commun.* **1994**, 1123. (g) Botteghi, C. *Gazz. Chim. Ital.* **1975**, *105*, 233. (h) Mori, K. *Tetrahedron* **1975**, *31*, 3011. (i) Schuler, H. R.; Slessor, K. N. *Can. J. Chem.* **1977**, *55*, 3280. For synthesis of the dihydrofuran, see: (j) Goldsmith, D. J.; Liotta, D. C.; Volmer, M.; Hoekstra, W.; Waykole, L. *Tetrahedron* **1985**, *41*, 4873. (k) Ducoux, J. P.; Le Menez, P.; Kunesch, N.; Wenkert, E. *J. Org. Chem.* **1993**, *58*, 1290.

(22) Purchased from the Aldrich Chemical Co.

0022-3263/96/1961-1119$12.00/0 

**Scheme 1**




Their exposure to a catalytic quantity of camphorsulfonic acid in $CH_2Cl_2$ at rt furnished a chromatographically separable 1:1 mixture of **9** and **10**. A likely explanation for the coproduction of both diastereomeric cyclohexanones is that the rates of 1,2-migration of the geminally substituted carbon in **A** and **B** are not influenced by the orientation of the methyl substituent resident on the oxonium ring and are therefore closely comparable.

No effort was expended in distinguishing **9** from **10** since their individual structures would be made clear upon accessing the theaspirones. The more polar diastereomer, subsequently identified as **10**, was transformed efficiently into enone **12** by oxidation of its silyl enol ether with palladium acetate in acetonitrile.[23] The yields for the conversion of **9** to **11** and of **10** to **12** are based on recovered starting materials. The final requisite carbon was introduced by reaction of **12** with methyllithium in the presence of anhydrous cerium trichloride.[24] Oxidation of the resulting carbinol with pyridinium chlorochromate proceeded with allylic rearrangement as expected[25] to give the targeted *cis*-theaspirone (**2**). Analogous treatment of **9** afforded **1** with closely comparable efficiency.

In agreement with reported data, **1** is a white solid, mp 58−59 °C, while **2** is a colorless liquid.[4] The spectral properties proved identical to those earlier reported, including corroborative NOE determinations which showed the vinylic methyl to be proximal to the ether proton in **2** but not in **1**.[26]

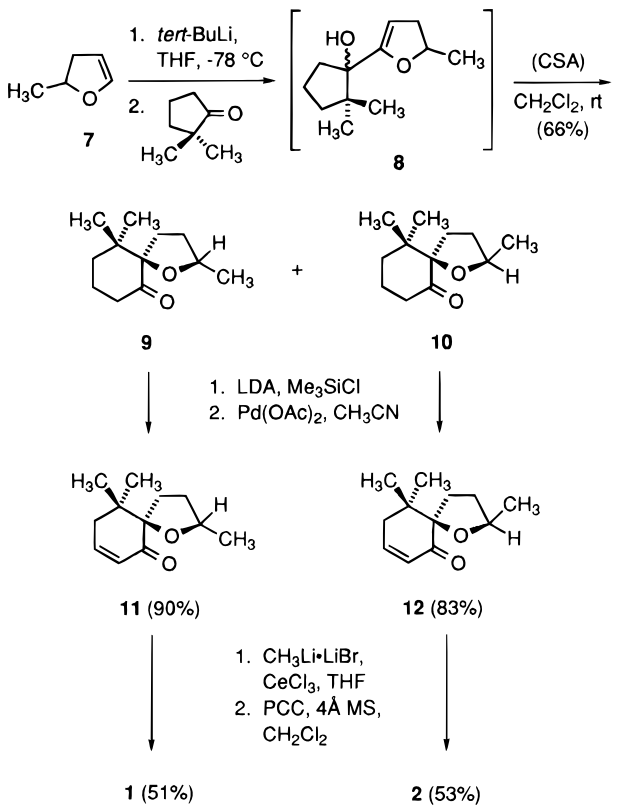
Thus, a concise synthesis of the two isomers of theaspirone has been achieved via a rearrangement scheme employing a small number of laboratory operations.

The approach establishes the feasibility of elaborating the spirotetrahydrofuran subunit without introducing impurities that might affect the olfactory properties of the end product.

## Experimental Section

See reference 15b for a listing of general experimental details.

**Scheme 2**




**2-Methyl-2,3-dihydrofuran (7).**[21j,k] Freshly distilled γ-valerolactone (9.37 g, 93.5 mmol) was dissolved in $CH_2Cl_2$ (200 mL), cooled to −78 °C under $N_2$, and treated dropwise during 1 h with a solution of diisobutylaluminum hydride in hexanes (125 mL of 1 M, 125 mmol). The reaction mixture was stirred at −78 °C for 1.5 h, quenched cautiously with a saturated solution of Rochelle's salt (100 mL), and stirred for 20 h while slowly being warmed to rt. The separated aqueous layer was extracted with ether and the combined organic phases were washed with a small amount of brine, dried, and concentrated to give the lactol as a colorless oil (8.95 g, 94%) that was used directly.

The lactol (8.95 g, 87.6 mmol) was dissolved in dry $CH_2Cl_2$ (100 mL), cooled to 0 °C under $N_2$, and treated with freshly distilled triethylamine (42.0 mL, 301 mmol). After 15 min of stirring, benzoyl chloride (11.60 mL, 117.2 mmol) was slowly introduced via syringe, and the reaction mixture was allowed to warm to rt during 15 h. Approximately half of the solvent was removed in vacuo, and the remaining solution was washed with 5% HCl and brine prior to drying and concentration in vacuo. The benzoate was obtained as a yellowish oil (18.01 g) which was pyrolyzed without further purification.

Into a Kugelrohr apparatus fitted with two traps was placed 4.74 g (23.0 mmol) of **6**. The first trap was cooled to −78 °C, the pressure was reduced to ca. 30 Torr, and the oven temperature was raised to 180 °C. After 1 h, the apparatus was allowed to cool and $N_2$ was bled in. The material in the −78 °C trap was redistilled at 30 Torr to give 1.410 g (73%) of **7** as a colorless oil: $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 6.24 (q, $J$ = 2.5 Hz, 1 H), 4.83 (q, $J$ = 2.5 Hz, 1 H), 4.66 (m, 1 H), 2.73 (m, 1 H), 2.19 (m, 1 H), 1.32 (d, $J$ = 6 Hz, 3 H); $^{13}$C NMR (75 MHz, $CDCl_3$) ppm 144.8, 98.8, 77.6, 36.3, 21.8.

**(2*R**,5*S**)-2,10,10-Trimethyl-1-oxaspiro[4.5]decan-6-one (9) and (2*R**,5*R**)-2,10,10-Trimethyl-1-oxaspiro[4.5]-decan-6-one (10).** A solution of **7** (801 mg, 9.53 mmol) in dry THF (45 mL) was cooled to −78 °C under argon and treated with *tert*-butyllithium (5.00 mL of 1.7 M in hexanes, 8.50 mmol). After 2 h of stirring, 2,2-dimethylcyclopentanone (1.00 mL, 7.65 mmol) was introduced via syringe, and the reaction mixture was stirred overnight, warmed to rt, and recooled to −78 °C prior to quenching with saturated $NaHCO_3$ solution

(23) Ito, Y.; Hirao, T.; Saegusa, T. *J. Org. Chem.* **1978**, *43*, 1011.
(24) Imamoto, T.; Takiyama, N.; Nakamura, K.; Hatajima, T.; Kamiya, Y. *J. Am. Chem. Soc.* **1989**, *111*, 4392.
(25) Dauben, W. G.; Michno, D. M. *J. Org. Chem.* **1977**, *42*, 682.
(26) Nakatani, Y.; Yamanishi, T.; Esumi, N.; Suzuki, T. *Agr. Biol. Chem.* **1970**, *34*, 152.

(5 mL). The aqueous phase was extracted with ether, and the combined organic phases were washed with brine, dried, and concentrated in vacuo. NMR analysis indicated that **8** consisted of a 1:1 mixture of diastereomers.

The above alcohols were dissolved in $CH_2Cl_2$ (40 mL), treated with camphorsulfonic acid (20 mg), stirred for 12 h, and concentrated to leave a semisolid. Chromatography of this material on silica gel (elution with 4:1 petroleum ether−ether) afforded a 1:1 mixture of **9** and **10** (993 mg, 66% overall). The isomerically pure ketones were obtained by flash chromatography (silica gel, elution with 5:1 petroleum ether−ether) with **9** being less polar than **10**.

For **9**: IR ($CHCl_3$, $cm^{-1}$) 1711, 1458, 1384, 1212, 1110, 1076; $^1H$ NMR (300 MHz, $C_6C_6$) $\delta$ 3.75−3.65 (m, 1 H), 2.86−2.76 (m, 1 H), 2.45−2.36 (m, 1 H), 2.15−2.08 (m, 1 H), 1.95−1.84 (m, 1 H), 1.74−1.64 (m, 1 H), 1.53−1.31 (m, 3 H), 1.13−0.92 (m, 2 H), 1.05 (d, $J$ = 6 Hz, 3 H), 0.90 (s, 3 H), 0.66 (s, 3 H); $^{13}C$ NMR 210.3, 92.9, 74.9, 40.3, 37.1, 35.8, 33.9, 25.0, 23.6, 22.2 (2 C), 20.7; MS $m/z$ ($M^+$) calcd 196.1463, obsd 196.1462. Anal. Calcd for $C_{12}H_{20}O_2$: C, 73.43; H, 10.27. Found: C, 73.63; H, 10.41.

For **10**: IR ($CHCl_3$, $cm^{-1}$) 1713, 1459, 1383, 1224, 1110, 1077; $^1H$ NMR (300 MHz, $C_6D_6$) $\delta$ 3.84−3.77 (m, 1 H), 3.00−2.89 (m, 1 H), 2.58−2.51 (m, 1 H), 2.17−2.10 (m, 1 H), 2.04−1.94 (m, 1 H), 1.62−1.21 (m, 4 H), 1.14−0.94 (m, 1 H), 1.03 (d, $J$ = 6 Hz, 3 H), 0.90−0.81 (m, 1 H), 0.88 (s, 3 H), 0.62 (s, 3 H); $^{13}C$ NMR (75 MHz, $C_6D_6$) ppm 210.0, 93.0, 77.7, 41.1, 37.2, 36.0, 34.6, 26.0, 23.9, 22.4, 21.6, 21.5; MS $m/z$ ($M^+$) calcd 196.1433, obsd 196.1433. Anal. Calcd for $C_{12}H_{20}O_2$: C, 73.43; H, 10.27. Found: C, 73.39; H, 10.29.

**(2*R**,5*S**)-2,10,10-Trimethyl-1-oxaspiro[4.5]dec-7-en-6-one (11).** To a solution of diisopropylamine (0.40 mL, 2.85 mmol) in dry THF (2.5 mL) cooled to −78 °C under argon was added 1.6 M *n*-butyllithium in hexanes (1.60 mL, 2.56 mmol). The reaction mixture was stirred at −78 °C for 1 h, treated with chlorotrimethylsilane (1.10 mL, 8.67 mmol) and 30 min later with **9** (165 mg, 0.84 mmol) dissolved in THF (0.80 mL), allowed to warm to rt over a period of 15 h, quenched with triethylamine (1.20 mL), and concentrated. Repeated trituration of the resulting semisolid with petroleum ether, filtration of the combined decanted solutions, and solvent evaporation afforded the silyl enol ether that was used without further purification.

The above material was dissolved in acetonitrile (15 mL) under argon, palladium acetate (215 mg, 0.96 mmol) was introduced, and the reaction mixture was stirred at rt until no starting material remained (72 h, TLC analysis). After solvent evaporation, the residue was subjected to flash chromatography on silica gel (elution with 5:1 petroleum ether−ether) to return 45 mg (27%) of **9** and furnish 103 mg (63% or 90% corrected) of **11** as a faintly yellow oil: IR ($CHCl_3$, $cm^{-1}$) 1684, 1470, 1386, 1103; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 6.73 (dt, $J$ = 10, 4 Hz, 1 H), 5.98 (dt, $J$ = 10, 1.5 Hz, 1 H), 4.18−4.08 (m, 1 H), 2.41 (br d, $J$ = 8 Hz, 1 H), 2.15 (br d, $J$ = 8 Hz, 1 H), 2.06−1.91 (m, 3 H), 1.60−1.52 (m, 1 H), 1.26 (d, $J$ = 6 Hz, 3 H), 1.05 (s, 3 H), 0.96 (s, 3 H); $^{13}C$ NMR (75 MHz, $CDCl_3$) ppm 199.7, 146.9, 127.4, 78.1, 77.2, 39.9, 39.7, 33.9, 33.8, 23.3, 22.9, 21.1; MS $m/z$ ($M^+$) calcd 194.1307, obsd 194.1307. Anal. Calcd for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34. Found: C, 73.89; H, 9.39.

***trans*-Theaspirone (1).** Cerium trichloride heptahydrate (1.64 g, 4.40 mmol) was dried under high vacuum (<1 Torr) while being heated at 100 °C for 1 h and at 140 °C for 12 h. After argon was bled in, dry THF (15 mL) was added, and the slurry was stirred for 5 h prior to being cooled to 0 °C. A solution of the methyllithium−lithium bromide complex in ether (2.80 mL of 1.5 M, 4.20 mmol) was introduced via syringe during 30 s, and the resulting yellow solution was stirred at 0 °C for 30 min before **11** (89 mg, 0.46 mmol) dissolved in THF (2 mL) was added. The reaction mixture was allowed to warm to rt during 12 h, quenched cautiously with brine (3 mL), and diluted with ether (20 mL). The separated organic phase was dried and concentrated to leave a residue which was purified by flash chromatography on silica gel (elution with 4:1 petroleum ether−ether). The diastereomeric alcohol mixture (70 mg, 73%) was oxidized without further processing.

Pyridinium chlorochromate (160 mg, 0.743 mmol) and powdered 4 Å molecular sieves (986 mg) were stirred in $CH_2Cl_2$ (2 mL) while the above alcohol mixture dissolved in $CH_2Cl_2$ (1 mL) was added. After 4 h of stirring, the reaction mixture was freed of solvent under reduced pressure, and the residue was subjected to flash chromatograhy on silica gel (elution with 22:3 petroleum ether−ether). There was obtained 49 mg (70%) of **1** as well as 7.2 mg (10%) of the less polar allylic alcohol diastereomer.

For **1**: colorless crystals, mp 58−59 °C; IR ($CHCl_3$, $cm^{-1}$) 1660, 1474, 1374, 1249, 1082; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 5.74 (d, $J$ = 1 Hz, 1 H), 4.25−4.19 (m, 1 H), 2.44−2.23 (m, 3 H), 2.18−2.08 (m, 1 H), 1.95 (d, $J$ = 1 Hz,3 H), 1.90−1.81 (m, 1 H), 1.68−1.55 (m, 1 H), 1.28 (d, $J$ = 6 Hz, 3 H), 1.05 (s, 3 H); 0.99 (s, 3 H); $^{13}C$ NMR (75 MHz, $CDCl_3$) ppm 198.7, 125.2, 88.5, 77.9, 49.9, 41.6, 35.0, 32.7, 32.6, 24.4, 23.7, 21.3, 20.4.

**(2*R**,5*R**)-2,10,10-Trimethyl-1-oxaspiro[4.5]dec-7-en-6-one (12).** Analogous processing of **10** (99 mg, 0.50 mmol) afforded 136 mg (100%) of the silyl enol ether, whose reaction with palladium acetate (75 mg, 0.33 mmol) in dry acetonitrile (1 mL) for 3 days gave 27 mg (41%) of recovered **10** and 32 mg (49% or 83% corrected) of **12** as a white solid: mp 118 °C dec; IR (neat, $cm^{-1}$) 1682, 1386, 1094; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 6.70 (dt, $J$ = 10.1, 4.0 Hz, 1 H), 5.94 (dt, $J$ = 10.1, 2.0 Hz, 1 H), 4.09 (m, 1 H), 2.40−1.8 4 (m, 5 H), 1.39−1.21 (m, 1 H), 1.20 (d, $J$ = 6.0 Hz, 3 H), 1.00 (s, 3 H), 0.93 (s, 3 H); $^{13}C$ NMR (75 MHz, $CDCl_3$) ppm 147.0, 127.3, 90.1, 76.1, 45.1, 40.0, 38.8, 33.7, 23.1, 22.8, 20.5 (carbonyl carbon not seen); MS $m/z$ ($M^+$) calcd 194.1307, obsd 194.1299.

***cis*-Theaspirone (2).** From dry cerium trichloride (1.9 mmol), methyllithium (1.9 mmol), and **12** (37 mg, 0.19 mmol), which were reacted as above, the tertiary carbinol was obtained as a yellow oil. Oxidation of this material with pyridium chlorochromate (83 mg, 0.38 mmol) in the presence of 4 Å molecular sieves (40 mg) followed by chromatography on silica gel (elution with 20:1 hexanes−ethyl acetate) gave **2** (21 mg, 53% overall) as a colorless oil: IR (neat, $cm^{-1}$) 1668, 1624, 1473, 1443, 1385, 1274, 1155, 1084, 972; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 5.71 (quintet, $J$ = 1.3 Hz, 1 H), 4.12 (septet, $J$ = 5.6 Hz, 1 H), 2.39 (dd, $J$ = 17.1, 0.7 Hz, 1 H), 2.35−2.26 (m, 1 H), 2.20 (dd, $J$ = 17.1, 1.3 Hz, 1 H), 2.06−1.95 (m, 1 H), 1.97 (d, $J$ = 1.3 Hz, 3 H), 1.84−1.73 (m, 1 H), 1.56−1.42 (m, 1 H), 1.30 (d, $J$ = 5.9 Hz, 3 H), 1.01 (s, 3 H), 0.97 (s, 3 H); $^{13}C$ NMR (75 MHz, $CDCl_3$) ppm 198.3, 168.3, 124.9, 88.5 77.7, 50.2, 40.8, 34.3, 32.7, 24.4, 23.0, 20.4, 18.9; MS $m/z$ ($M^+$) calcd 208.1463, obsd 208.1474.

**Acknowledgment.** These studies have been supported by a grant from the Hoechst Marion Roussel Co. We are indebted to Professor C. C. Liao (National Tsing Hua University) for enabling arrangements in connection with H.-L. Wang's visit.

JO951890H