leading to racemic **9** and *meso*-**10** by an analogous process. In the event, the catalytic hydrogenation of **6** proceeded smoothly over Rh on carbon, which gave more reproducible results, furnishing an inseparable mixture of **9** and **10** (entry 10). Although variable optical rotations were obtained, analysis of the $^1H$ NMR spectrum after the addition of the chiral shift reagent (+)-Eu(tfc)$_3$[9] gave rise to a similar splitting of the *N*-tosyl methyl resonances to that shown with the secondary amines derived from racemic nitrile (*rac*-**6**), prepared from *rac*-valine. The ratio between the *d*, *l* and *meso* secondary amines was estimated to be approximately 1:1 by integration of the NH protons of the corresponding *N*-acetyl derivatives in a $^1H$ NMR spectrum measured at 50 °C in $(CD_3)_2SO$. At lower temperatures or in deuteriochloroform solutions the spectra were complicated by the presence of several rotamers. Similarly, the presence of amide rotamers precluded any accurate determination of the diastereoisomeric excess based on the analysis of the $^1H$ or $^{19}F$ NMR spectra of the derived Mosher amides.[10]

In summary, the catalytic hydrogenation of nitriles to secondary amines under ambient conditions has been described. This synthetic method could be particularly useful for the rapid assemblage of functionalized subunits in the preparation of macrocyclic structures.

## Experimental Section

**General Procedure for the Catalytic Hydrogenation of Nitriles.** A mixture of nitrile (0.35 mmol) in glacial acetic acid (3 mL) and 5% rhodium on alumina (400 mg) was stirred at 23 °C under 1 atm of $H_2$ for 24–30 h. The progress of the reaction was monitored by TLC. The resulting suspension was filtered through Celite, and the filtrate was partitioned between dichloromethane and saturated aqueous sodium bicarbonate solution. In entries 6 and 7 the crude secondary amine was treated with 1 M HCl in methanol at 23 °C for 1 h, followed by evaporation of the solvent to give the amine hydrochloride. Isolated yields of pure amines are shown in Table I.

**Acknowledgment.** This work was supported by the "Comisión Asesora de Investigación Científica y Técnica" (CAICYT, Grant 84-0410). We gratefully acknowledge Prof. J. Elguero for a gift of 3-cyano-1-methylpyrazole and A. Salmerón for some hydrogenation experiments.

**Supplementary Material Available:** Experimental details and spectroscopic data for (*S*)- and (*R*,*S*)-*N*-tosylvaline, *N*-tosylvalinamide, and the compounds in Table I and $^1H$ NMR and COSY spectra for amine 4 (9 pages). Ordering information is given on any current masthead page.

(9) (+)-Eu(tfc)$_3$ = europium(III) tris[3-(trifluoromethylhydroxymethylene)-(+)-camphorato].

(10) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543.

# Synthesis of Castasterone and Formal Synthesis of Brassinolide from Stigmasterol via a Selenosulfonation Approach

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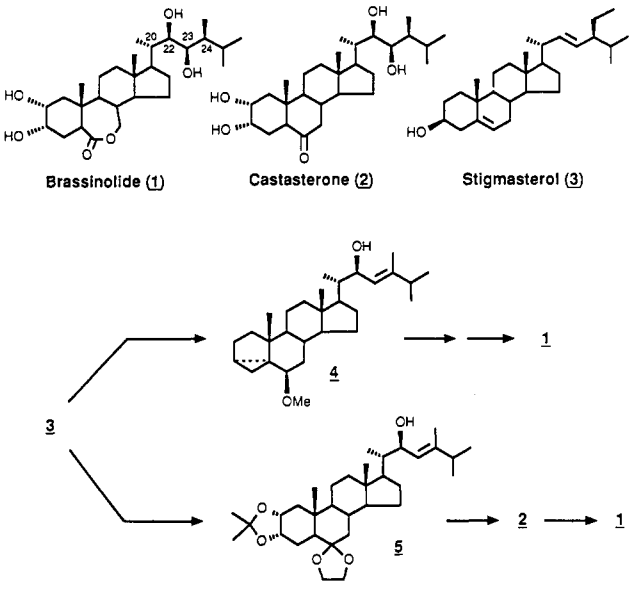
*Received May 14, 1990*

Brassinolide (**1**) is a steroidal plant growth-promoter that was first isolated by Grove and co-workers[1] from *Brassica napus* L. pollen in 1979. Its low abundance in natural sources and intriguing structure have made it the target of several syntheses.[2,3] The unusual B-ring lactone and the four contiguous chiral centers at C-20, C-22, C-23, and C-24, including the vicinal diol at C-22 and C-23, are structural features that require special attention. Certain related sterols such as castasterone (**2**) exhibit similar activity,[4] and their syntheses are also of interest.[3c,f,k]

**Scheme I**




We recently reported the preparation of the allylic alcohol **4** from stigmasterol (**3**)[5] using selenosulfonation methodology.[6] Alcohol **4** has also been prepared by other methods[3a,n] and is a useful intermediate for the elaboration of brassinosterol side chains. We now report the selenosulfonation-based preparation of the more highly elaborated intermediate **5**, which provides more direct access

(1) Grove, M. D.; Spencer, G. F.; Rohwedder, W. K.; Mandava, N.; Worley, J. F.; Warthen, J. D., Jr.; Steffens, G. L.; Flippen-Anderson, J. L.; Cook, J. C., Jr. *Nature (London)* **1979**, *281*, 216.

(2) For reviews of brassinosteroids, see: (a) Chen, S. C. *Chem. Can.* **1983**, *35* (September), 13. (b) Singh, H.; Bhardwaj, T. R. *Indian J. Chem., Sect. B* **1986**, *25B*, 989.

(3) For previous syntheses of brassinolide, see: (a) Fung, S.; Siddall, J. B. *J. Am. Chem. Soc.* **1980**, *102*, 6580. (b) Ishiguro, M.; Takatsuto, S.; Morisaki, M.; Ikekawa, N. *J. Chem. Soc., Chem. Commun.* **1980**, 962. (c) Takatsuto, S.; Yazawa, N.; Ishiguro, M.; Morisaki, M.; Ikekawa, N. *J. Chem. Soc., Perkin Trans. 1* **1984**, 139. (d) Mori, K.; Sakakibara, M.; Ichikawa, Y.; Ueda, H.; Okada, K.; Umemura, T.; Yabuta, G.; Kuwahara, S.; Kondo, M.; Minobe, M.; Sogabe, A. *Tetrahedron* **1982**, *38*, 2099. (e) Sakakibara, M.; Okada, K.; Ichikawa, Y.; Mori, K. *Heterocycles* **1982**, *17*, 301. (f) Mori, K.; Sakakibara, M.; Okada, K. *Tetrahedron* **1984**, *40*, 1767. (g) Sakakibara, M.; Mori, K. *Agric. Biol. Chem.* **1983**, *47*, 663. (h) Thompson, M. J.; Mandava, N. B.; Meudt, W. J.; Lusby, W. R.; Spaulding, D. W. *Steroids* **1981**, *38*, 567. (i) Donaubauer, J. R.; Greaves, A. M.; McMorris, T. C. *J. Org. Chem.* **1984**, *49*, 2833. (j) Kametani, T.; Katoh, T.; Tsubuki, M.; Honda, T. *J. Am. Chem. Soc.* **1986**, *108*, 7055. (k) Kametani, T.; Katoh, T.; Fujio, J.; Nogiwa, I.; Tsubuki, M.; Honda, T. *J. Org. Chem.* **1988**, *53*, 1982. (l) Kametani, T.; Kigawa, M.; Tsubuki, M.; Honda, T. *J. Chem. Soc., Perkin Trans. 1* **1988**, 1503. (m) Wei-Shan, Z.; Jiang, B.; Pan, X. *J. Chem. Soc., Chem. Commun.* **1989**, 612. (n) Anastasia, M.; Allevi, P.; Ciuffreda, P.; Fiecchi, A.; Scala, A. *J. Org. Chem.* **1984**, *49*, 4297. (o) Anastasia, M.; Ciuffreda, P.; Fiecchi, A. *J. Chem. Soc., Perkin Trans. 1* **1983**, 379.

(4) (a) Takatsuto, S.; Yazawa, N.; Ikekawa, N.; Takematsu, T.; Takeuchi, Y.; Koguchi, M. *Phytochem.* **1983**, *22*, 2437. (b) Thompson, M. J.; Meudt, W. J.; Mandava, N. B.; Dutky, S. R.; Lusby, W. R.; Spaulding, D. W. *Steroids* **1982**, *39*, 89.

(5) Back, T. G.; Brunner, K.; Krishna, M. V.; Lai, E. K. Y. *Can. J. Chem.* **1989**, *67*, 1032.

(6) (a) Back, T. G. In *Organoselenium Chemistry*; Liotta, D., Ed.; Wiley: New York, 1987; Chapter 7, pp 347–354. (b) Back, T. G. In *The Chemistry of Organic Selenium and Tellurium Compounds*; Patai, S., Ed.; Wiley: Chichester, 1987; Volume 2, Chapter 3, pp 136–138.

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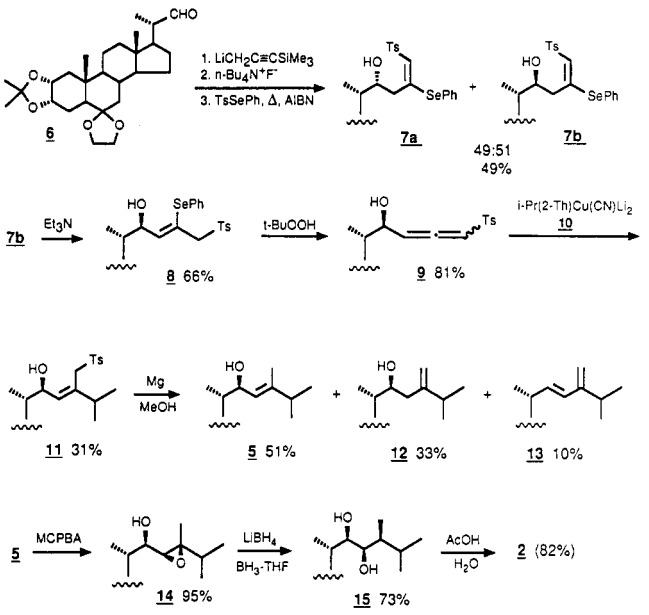
**Scheme II**[a]




[a] (**a**) Ts = *p*-tolylsulfonyl, (**b**) 2-Th = 2-thienyl.

to castasterone (**2**) (Scheme I) and which was previously employed in the preparation of dolichosterone.[3f] Since the conversion of castasterone (**2**) to brassinolide (**1**) has been previously reported,[3a,c,d] the present work also constitutes a formal synthesis of **1**.

Our approach is shown in Scheme II. The aldehyde **6** was readily obtained from stigmasterol (**3**).[3d] The addition of 3-lithio-1-(trimethylsilyl)propyne[7] to **6**, followed by desilylation with tetra-*n*-butylammonium fluoride and selenosulfonation of the resulting acetylene with *Se*-phenyl *p*-tolueneselenosulfonate,[8] afforded the corresponding C-22 epimers **7a** and **7b** in 49% overall yield in the ratio of 49:51. After separation from **7a** by preparative TLC or flash chromatography, the more polar epimer **7b** was isomerized to the allyl sulfone **8** and subjected to selenoxide syn elimination to produce the allene **9**.[9] The latter was obtained as a mixture of diastereomers that did not require separation and could be employed as such in the next step. The required isopropyl group was introduced by the addition of the organocuprate reagent **10**[10] to the less hindered face of the sulfonyl-substituted $\pi$-bond of allene **9**. The desired *Z* isomer of **11** was obtained with high stereoselectivity but in relatively low yield because of competing elimination to produce diene byproducts. Reductive desulfonylation of **11** was achieved with magnesium in methanol,[11] affording the desired allylic alcohol **5** as the principal product, along with the homoallylic isomer **12** and the diene **13**.

The conversion of **5** to castasterone (**2**) was straightforward and based on literature precedents. Stereoselective epoxidation of **5** with *m*-chloroperbenzoic acid (MCPBA) produced **14**,[3f] which was reduced to diol **15** with lithium borohydride and borane–THF.[12] Deprotection under standard conditions afforded **2**, which had physical and spectral properties in close agreement with literature values.[3c,f]

## Experimental Section

Melting points were determined on an A. H. Thomas hot-stage apparatus and are uncorrected. IR spectra were recorded on a Nicolet 5DX spectrometer as films. $^1H$ and $^{13}C$ NMR spectra were recorded on a Bruker ACE 200 or a Bruker AM 400 spectrometer, operating at 200 and 400 MHz, respectively, in deuteriochloroform solvent with either chloroform or tetramethylsilane as the internal standard. Mass spectra were recorded on a Kratos MS80 or a VG 7070 spectrometer. Elemental analyses were obtained by Ms. D. Fox and Dr. R. Yamdagni at the University of Calgary or by Guelph Chemical Laboratories. Preparative TLC was carried out on Analtech 20 × 20 cm glass plates coated with 1 mm of silica gel GF and analytical TLC on Merck silica gel 60 F-254 sheets. Flash chromatography was performed on Merck silica gel, 60–200 mesh. *Se*-Phenyl *p*-tolueneselenosulfonate was prepared by a literature method.[13] All other reagents were purchased from commercial sources and were purified by standard methods as required.

**(2*R*,3*S*,22*R*,24*E*)-6,6-(Ethylenedioxy)-2,3-(isopropylidenedioxy)-24-(phenylseleno)-25-(*p*-tolylsulfonyl)-(5$\alpha$)-26,27-dinorcholest-24-en-22-ol (7a) and the 22*S* Epimer 7b.** *n*-Butyllithium in hexane (1.35 mmol) was added to a solution of 1-(trimethylsilyl)propyne (200 $\mu$L, 1.35 mmol) in 1.5 mL of THF at 0 °C. After 10 min the solution was cooled to −30 °C and aldehyde **6** (200 mg, 0.45 mmol) in 1 mL of THF was added dropwise. The mixture was stirred at −30 °C for 12 h, then gradually warmed to room temperature, diluted with ether, washed with aqueous NaCl, dried ($MgSO_4$), and evaporated in vacuo. The product was stirred with tetra-*n*-butylammonium fluoride (0.8 mmol) in 5 mL of THF at 0 °C for 25 min. The solution was again diluted with ether and worked up as before to afford the desilylated product, which was used directly in the following selenosulfonation step without further purification.

The latter product and *Se*-phenyl *p*-tolueneselenosulfonate (140 mg, 0.45 mmol) were refluxed for 24 h in 2 mL of benzene containing ca. 2 mg of azobis(isobutyronitrile) (AIBN). Preparative TLC (8% acetonitrile–dichloromethane) afforded 85 mg (24%) of the less polar C-22 epimer **7a** and 89 mg (25%) of the more polar epimer **7b**.[14]

Compound **7a** was a pale yellow oil: $R_f$ 0.55 (8% acetonitrile–dichloromethane); IR (film) 3506, 1596, 1367, 1303, 1291, 1144, 1084, 1055, 733 cm$^{-1}$; $^1H$ NMR (200 MHz) $\delta$ 7.68 (d, $J$ = 8.4 Hz, 2 H), 7.57–7.27 (complex, 7 H), 6.03 (s, 1 H), 4.27 (m, 1 H), 4.2–3.7 (m, 5 H), 3.45 (dd, $J$ = 14.0, 11.0 Hz, 1 H), 3.18 (d, $J$ = 8.0 Hz, 1 H), 2.43 (s, 3 H), 1.48 (s, 3 H), 1.33 (s, 3 H), 1.01 (d, $J$ = 6.6 Hz, 3 H), 0.84 (s, 3 H), 0.71 (s, 3 H); mass spectrum, $m/z$ (relative intensity) 780 ($M^+$ − 18, 0.2), 431 (62), 387 (38), 235 (91), 155 (88), 93 (100). Anal. Calcd for $C_{43}H_{58}O_7SSe$: C, 64.71; H, 7.34. Found: C, 64.51; H, 7.11.

Compound **7b** was a pale yellow oil: $R_f$ 0.36 (8% acetonitrile–dichloromethane); IR (film) 3491, 1596, 1367, 1303, 1291, 1144, 1085, 733 cm$^{-1}$; $^1H$ NMR (200 MHz) $\delta$ 7.67 (d, $J$ = 8.3 Hz, 2 H), 7.56–7.25 (complex, 7 H), 5.98 (s, 1 H), 4.27 (m, 1 H), 4.20–3.7 (m, 5 H), 3.43 (dd, $J$ = 14.1, 10.2 Hz, 1 H), 2.42 (s, 3 H), 1.48 (s, 3 H), 1.33 (s, 3 H), 0.98 (d, $J$ = 6.3 Hz, 3 H), 0.84 (s, 3 H), 0.68 (s, 3 H); mass spectrum, $m/z$ (relative intensity) 431 (71), 235 (100), 155 (75), 93 (92). Anal. Calcd for $C_{43}H_{58}O_7SSe$: C, 64.71; H, 7.34. Found: C, 64.69; H, 7.54.

**(2*R*,3*S*,22*R*,23*Z*)-6,6-(Ethylenedioxy)-2,3-(isopropylidenedioxy)-24-(phenylseleno)-25-(*p*-tolylsulfonyl)-(5$\alpha$)-26,27-dinorcholest-23-en-22-ol (8).** Compound **7b** (420 mg, 0.53 mmol) was refluxed for 48 h in a mixture of 5 mL of triethylamine and 15 mL of toluene. After removal of volatile material in vacuo, flash chromatography of the residue (elution with 12% acetonitrile–dichloromethane) produced 275 mg (66%)

(7) Corey, E. J.; Kirst, H. A. *Tetrahedron Lett.* **1968**, 5041.

(8) (a) Back, T. G.; Collins, S.; Kerr, R. G. *J. Org. Chem.* **1983**, *48*, 3077. (b) Back, T. G.; Collins, S.; Gokhale, U.; Law, K.-W. *J. Org. Chem.* **1983**, *48*, 4776. (c) Miura, T.; Kobayashi, M. *J. Chem. Soc., Chem. Commun.* **1982**, 438.

(9) For a general preparation of allenes and allenic sulfones from acetylenes using selenosulfonation, see: Back, T. G.; Krishna, M. V.; Muralidharan, K. R. *J. Org. Chem.* **1989**, *54*, 4146.

(10) Lipshutz, B. H.; Koerner, M.; Parker, D. A. *Tetrahedron Lett.* **1987**, *28*, 945.

(11) Brown, A. C.; Carpino, L. A. *J. Org. Chem.* **1985**, *50*, 1749.

(12) The elaboration of the side chain of **4** by epoxidation and hydride reduction was reported by Fung and Siddall (ref 3a).

(13) Back, T. G.; Collins, S.; Krishna, M. V. *Can. J. Chem.* **1987**, *65*, 38.

(14) When the preparation of **7a,b** was repeated with up to 3 mmol of aldehyde **6**, the overall yields were in the range 39–45%.

of **8** as a solid foam: $R_f$ 0.39 (10% acetonitrile–dichloromethane); IR (film) 3468, 1598, 1318, 1303, 1140, 1086, 1056, 911, 734 $cm^{-1}$; $^1H$ NMR (200 MHz) $\delta$ 7.69 (d, $J$ = 8.3 Hz, 2 H), 7.36–7.24 (complex, 7 H), 6.22 (d, $J$ = 7.2 Hz, 1 H), 4.64 (m, 1 H), 4.27 (m, 1 H), 4.11 (m, 1 H), 3.98–3.71 (m, 6 H), 2.46 (s, 3 H), 1.48 (s, 3 H), 1.33 (s, 3 H), 0.87 (d, $J$ = 7.3 Hz, 3 H), 0.85 (s, 3 H), 0.67 (s, 3 H); mass spectrum, $m/z$ (relative intensity) 446 (6), 431 (33), 235 (90), 91 (100).

**(2*R*,3*S*,22*R*)-6,6-(Ethylenedioxy)-2,3-(isopropylidenedioxy)-25-(*p*-tolylsulfonyl)-(5α)-26,27-dinorcholesta-23,24-dien-22-ol (9).** The allylic sulfone **8** (126 mg, 0.16 mmol) and *tert*-butyl hydroperoxide (1.6 mL of a ca. 90% solution in *tert*-butyl alcohol) were stirred for 10 h in 10 mL of chloroform. Volatile material was then removed in vacuo and the residue was separated by flash chromatography (elution with 30% acetonitrile–dichloromethane) to afford 82 mg (81%) of the allenic sulfone **9** as a pale yellow oil: $R_f$ 0.42 (12% acetonitrile–dichloromethane); IR (film) 3468, 1956, 1598, 1319, 1304, 1216, 1147, 1086, 1056, 752 $cm^{-1}$; $^1H$ NMR (200 MHz) $\delta$ 7.78 (d, $J$ = 8 Hz, 2 H), 7.32 (d, $J$ = 8 Hz, 2 H), 6.31 (m, 1 H), 5.87 (m, 1 H), 4.43 (m, 1 H), 4.25 (m, 1 H), 4.09 (m, 1 H), 3.97–3.70 (m, 4 H), 2.42 (s, 3 H), 1.46 (s, 3 H), 1.31 (s, 3 H), 0.82 (s, 3 H), 0.66 and 0.65 (2 s, mixture of diastereomers, total 3 H); mass spectrum, $m/z$ (relative intensity) 640 ($M^+$, 0.4), 625 (1.7), 431 (48), 235 (78), 155 (38), 91 (87), 43 (100). Anal. Calcd for $C_{37}H_{52}O_7S$: C, 69.32; H, 8.18. Found: C, 68.82; H, 7.98.

**(2*R*,3*S*,22*R*,23*Z*)-6,6-(Ethylenedioxy)-2,3-(isopropylidenedioxy)-28-(*p*-tolylsulfonyl)-(5α)-ergost-23-en-22-ol (11).** A solution of 1.17 mmol of lithium (2-thienyl)cyanocuprate[10] in 12 mL of THF was cooled to −78 °C. Isopropyllithium (0.94 mmol) in petroleum ether was added, followed by the allenic sulfone **9** (150 mg, 0.234 mmol) in 2 mL of THF. After stirring for 30 min at −78 °C, the reaction was quenched with aqueous $NH_4Cl$ solution, dried ($MgSO_4$), filtered through Celite, and evaporated in vacuo. The residue was separated by preparative TLC in 12% acetonitrile–dichloromethane to afford 49 mg (31%) of **11** as a pale yellow oil: $R_f$ 0.49 (same solvent); IR (film) 3499, 1598, 1316, 1303, 1216, 1142, 1087, 1057, 755 $cm^{-1}$; $^1H$ NMR (200 MHz) $\delta$ 7.78 (d, $J$ = 8 Hz, 2 H), 7.36 (d, $J$ = 8 Hz, 2 H), 5.71 (d, $J$ = 7.0 Hz, 1 H), 4.26 (m, 2 H), 4.10–3.76 (m, 7 H), 2.46 (s, 3 H), 1.48 (s, 3 H), 1.33 (s, 3 H), 1.02 (d, $J$ = 7.1 Hz, 3 H), 0.98 (d, $J$ = 7.3 Hz, 3 H), 0.95 (d, $J$ = 6.9 Hz, 3 H), 0.83 (s, 3 H), 0.66 (s, 3 H); $^{13}C$ NMR $\delta$ 144.9 (C), 136.6 (C), 134.6 (C), 133.8 (CH), 129.8 (CH), 128.2 (CH), 109.6 (C), 107.5 (C), 72.9 (CH), 72.8 (CH), 70.6 (CH), 65.5 ($CH_2$), 64.1 ($CH_2$), 58.0 ($CH_2$), 55.7 (CH), 52.9 (CH), 52.2 (CH), 45.5 (CH), 42.7 ($CH_2$), 42.3 (C), 41.4 (CH), 41.0 ($CH_2$), 39.5 ($CH_2$), 38.0 (C), 34.3 (CH), 32.9 (CH), 28.6 ($CH_3$), 27.8 ($CH_2$), 26.5 ($CH_3$), 24.1 ($CH_2$), 22.2 ($CH_3$), 21.9 ($CH_2$), 21.6 ($CH_3$), 21.5 ($CH_3$) 20.7 ($CH_2$), 13.3 ($CH_3$), 12.3 ($CH_3$), 11.9 ($CH_3$); mass spectrum, $m/z$ (relative intensity) 669 ($M^+$ − 15, 0.4), 666 ($M^+$ − 18, 0.7), 513 (4), 387 (17), 329 (25), 235 (27), 178 (35), 91 (61), 43 (100).

**(2*R*,3*S*,22*R*,23*E*)-6,6-(Ethylenedioxy)-2,3-(isopropylidenedioxy)-(5α)-ergost-23-en-22-ol (5).** Magnesium turnings (80 mg, 3.33 mg atoms) in 6 mL of methanol were warmed to 40–50 °C. When hydrogen evolution commenced, the allylic sulfone **11** (48 mg, 0.070 mmol) was added in 1 mL of THF. The mixture was stirred at room temperature for 4 h until almost all of the magnesium disappeared. The mixture was concentrated under reduced pressure, 3 mL of 20% aqueous $NH_4Cl$ was added, and the product was extracted three times with ether, dried ($MgSO_4$), and evaporated in vacuo. Flash chromatography of the residue (elution with 4% acetone–hexane) afforded the following in order of elution.

(A) Diene **13** (4 mg, 10%) as a pale yellow oil: $R_f$ 0.69 (25% acetone–hexane); IR (film) 1643, 1604, 1239, 1216, 1174, 1054, 757 $cm^{-1}$; $^1H$ NMR (200 MHz) $\delta$ 5.93 (d, $J$ = 15.8 Hz, 1 H), 5.56 (dd, $J$ = 15.8, 8.6 Hz, 1 H), 4.84 (s, 1 H), 4.82 (s, 1 H), 4.27 (m, 1 H), 4.10 (m, 1 H), 4.0–3.71 (m, 4 H), 2.55 (m, 1 H), 1.48 (s, 3 H), 1.33 (s, 3 H), 1.08 (d, $J$ = 6.7 Hz, 3 H), 1.06 (d, $J$ = 6.8 Hz, 3 H), 1.05 (d, $J$ = 5.9 Hz, 3 H), 0.84 (s, 3 H), 0.70 (s, 3 H); mass spectrum, $m/z$ (relative intensity) 512 ($M^+$, 11), 497 ($M^+$ − 15, 23), 387 (80), 329 (62), 301 (47), 123 (90), 43 (100); exact mass calcd for $C_{33}H_{52}O_4$ 512.3866, found 512.3860.

(B) Homoallylic alcohol **12** (12 mg, 33%) as a pale yellow oil: $R_f$ 0.43 (25% acetone–hexane); IR (film) 3492, 1639, 1244, 1216, 1174, 1057, 909, 734 $cm^{-1}$; $^1H$ NMR (200 MHz) $\delta$ 4.89 (s, 1 H), 4.79 (s, 1 H), 4.27 (m, 1 H), 4.10 (m, 1 H), 3.98–3.7 (m, 5 H), 1.48 (s, 3 H), 1.33 (s, 3 H), 1.06 (d, $J$ = 6.8 Hz, 3 H), 1.03 (d, $J$ = 6.8 Hz, 3 H), 0.94 (d, $J$ = 6.3 Hz, 3 H), 0.84 (s, 3 H), 0.67 (s, 3 H); $^{13}C$ NMR $\delta$ 153.3 (C), 109.7 (C), 109.3 ($CH_2$), 107.6 (C), 73.0 (CH), 72.9 (CH), 70.6 (CH), 65.5 ($CH_2$), 64.2 ($CH_2$), 55.8 (CH), 53.0 (CH), 52.8 (CH), 45.5 (CH), 42.7 ($CH_2$), 42.4 (C), 41.1 ($CH_2$ × 2 ?); 40.4 (CH), 39.7 ($CH_2$), 38.0 (C), 33.5 (CH), 33.0 (CH), 28.6 ($CH_3$), 27.7 ($CH_2$), 26.6 ($CH_3$), 24.1 ($CH_2$), 22.1 ($CH_3$), 22.0 ($CH_2$), 21.7 ($CH_3$), 20.8 ($CH_2$), 13.4 ($CH_3$), 11.93 ($CH_3$), 11.87 ($CH_3$); mass spectrum, $m/z$ (relative intensity) 530 ($M^+$, 2), 515 ($M^+$ − 15, 10), 431 (36), 389 (20), 319 (38), 235 (66), 149 (73), 99 (68), 43 (100); exact mass calcd for $C_{33}H_{54}O_5$ 530.3971, found 530.3990.

(C) Title compound **5**[3f] (19 mg, 51%) as a pale yellow oil: $R_f$ 0.39 (25% acetone–hexane); IR (film) 3491, 1663, 1216, 1058, 756 $cm^{-1}$; $^1H$ NMR (200 MHz) $\delta$ 5.32 (d, $J$ = 7.8 Hz, 1 H), 4.46 (d, $J$ = 7.7 Hz, 1 H), 4.26 (m, 1 H), 410 (m, 1 H), 3.92 (m, 3 H), 3.76 (m, 1 H), 1.61 (d, $J$ = 1.1 Hz, 3 H), 1.48 (s, 3 H), 1.33 (s, 3 H), 1.00 (d, $J$ = 6.8 Hz, 6 H), 0.95 (d, $J$ = 6.0 Hz, 3 H), 0.84 (s, 3 H), 0.67 (s, 3 H); $^{13}C$ NMR $\delta$ 142.8 (C), 124.8 (CH), 109.7 (C), 107.6 (C), 73.0 (CH), 72.9 (CH), 70.5 (CH), 65.5 ($CH_2$), 64.2 ($CH_2$), 55.8 (CH), 53.0 (CH), 52.6 (CH), 45.5 (CH), 42.7 ($CH_2$), 42.5 (C), 41.8 (CH), 41.1 ($CH_2$), 39.6 ($CH_2$), 38.0 (C), 36.7 (CH), 33.0 (CH), 28.6 ($CH_3$), 27.8 ($CH_2$), 26.6 ($CH_3$), 24.20 ($CH_2$), 22.0 ($CH_2$), 21.4 ($CH_3$), 21.3 ($CH_3$), 20.8 ($CH_2$), 14.2 ($CH_3$), 13.4 ($CH_3$), 12.3 ($CH_3$), 11.9 ($CH_3$); mass spectrum, $m/z$ (relative intensity) 530 ($M^+$, 0.5), 512 ($M^+$ − 18, 55), 497 (32), 387 (61), 123 (67), 43 (100).

**Castasterone (2).** Allylic alcohol **5** was converted into epoxide **14** with MCPBA in 95% yield by the method of Mori.[3f]

Compound **14** (19 mg, 0.035 mmol) in 1 mL of THF was added to a stirred mixture of lithium borohydride (4 mg, 0.17 mmol) and 0.17 mmol of borane–THF in 1 mL of THF at 0 °C. The mixture was stirred for 12 h at 0 °C and then quenched with water. The mixture was diluted with chloroform, washed with aqueous potassium carbonate, dried ($MgSO_4$), and evaporated in vacuo. Flash chromatography (elution with 5% acetone–hexane) afforded 14 mg (73%) of diol **15**[15] as an oil: $R_f$ 0.30 (30% acetone–hexane); IR (film) 3446, 1216, 1057, 734 $cm^{-1}$; $^1H$ NMR (200) $\delta$ 4.27 (m, 1 H), 4.10 (m, 1 H), 3.93 (m, 3 H), 3.75 (m, 2 H), 3.55 (m, 1 H), 1.48 (s, 3 H), 1.33 (s, 3 H), 0.97 (d, $J$ = 6.6 Hz, 3 H), 0.95 (d, $J$ = 6.8 Hz, 3 H), 0.90 (d, $J$ = 6.1 Hz, 3 H), 0.85 (d, $J$ = 5.3 Hz, 3 H), 0.84 (s, 3 H), 0.68 (s, 3 H); $^{13}C$-NMR $\delta$ 109.7 (C), 107.6 (C), 74.8 (CH), 73.5 (CH), 73.0 (CH), 72.9 (CH), 65.5 ($CH_2$), 64.2 ($CH_2$), 55.8 (CH), 52.9 (CH), 52.4 (CH), 45.5 (CH), 42.7 ($CH_2$), 42.3 (C), 41.0 ($CH_2$), 40.0 (CH), 39.7 ($CH_2$), 38.0 (C), 36.8 (CH), 33.0 (CH), 30.8 (CH), 29.3 ($CH_3$), 28.6 ($CH_3$), 27.7 ($CH_2$), 26.6 ($CH_3$), 24.0 ($CH_2$), 22.0 ($CH_2$), 20.9 ($CH_3$), 20.8 ($CH_2$), 20.7 ($CH_3$), 13.4 ($CH_3$), 11.9 ($CH_3$), 10.1 ($CH_3$); mass spectrum, $m/z$ (relative intensity) 548 ($M^+$, 22), 533 ($M^+$ − 15, 46), 431 (100), 389 (84), 337 (59), 43 (97).

Diol **15** (23 mg, 0.042 mmol) was dissolved in 1 mL of 80% aqueous acetic acid and warmed at 50 °C for 30 min. The solution was poured into aqueous sodium carbonate and extracted three times with chloroform. The chloroform solution was dried ($MgSO_4$) and evaporated in vacuo to give 16 mg (82%) of castasterone (**2**), mp 248–53 °C, from ethyl acetate (lit.[3c] mp 250–2 °C): IR 3379, 1708, 1216 $cm^{-1}$; $^1H$ NMR (400 MHz) $\delta$ 4.05 (m, 1 H), 3.79–3.70 (m, 2 H), 3.57–3.54 (m, 1 H), 2.69 (dd, $J$ = 12.6, 2.9 Hz, 1 H), 2.30 (dd, $J$ = 13.1, 4.5 Hz, 1 H), 0.97 (d, $J$ = 6.8 Hz, 3 H), 0.95 (d, $J$ = 6.8 Hz, 3 H), 0.91 (d, $J$ = 6.6 Hz, 3 H), 0.85 (d, $J$ = 6.9 Hz, 3 H), 0.76 (s, 3 H), 0.69 (s, 3 H); $^{13}C$ NMR $\delta$ 211.9 (C=O), 74.7 (CH), 73.6 (CH), 68.4 (CH), 68.3 (CH), 56.6 (CH), 53.7 (CH), 52.3 (CH), 50.7 (CH), 46.7 ($CH_2$), 42.8 (C), 42.6 (C), 40.2 ($CH_2$), 40.1 (CH), 39.4 ($CH_2$), 37.7 (CH), 36.8 (CH), 30.8 (CH), 27.6 ($CH_2$), 26.3 ($CH_2$), 23.8 ($CH_2$), 21.2 ($CH_2$), 20.9 ($CH_3$), 20.7 ($CH_3$), 13.6 ($CH_3$), 11.93 ($CH_3$), 11.90 ($CH_3$), 10.1 ($CH_3$); mass spectrum, $m/z$ (relative intensity) 464 ($M^+$, 0.4), 446 ($M^+$ − 18, 0.5), 43 (100).

**Acknowledgment.** We thank the Natural Sciences and Engineering Research Council of Canada for financial support.

(15) Sumitomo Chemical Co., Jpn. Kokai Tokkyo Koho JP 5933300 (Feb. 23, 1984); *Chem. Abstr.* **1984**, *101*, 111269t.

**Registry No.** 1, 72962-43-7; 2, 80736-41-0; 3, 83-48-7; 5, 93488-33-6; 6, 81481-15-4; 7a, 130200-10-1; 7b, 130200-11-2; 8, 130200-12-3; 9 (isomer 1), 130200-13-4; 9 (isomer 2), 130200-14-5; 10, 130219-71-5; 11, 130200-15-6; 12, 130200-16-7; 13, 130200-17-8; 14, 93488-34-7; 15, 91708-76-8; TsSePh, 68819-94-3; 1-(trimethylsilyl)propyne, 6224-91-5.

## A New Synthesis of Primary Aliphatic Amines by N,N-Didebenzylation. Synthesis of a Pirmenol (CI-845) Metabolite

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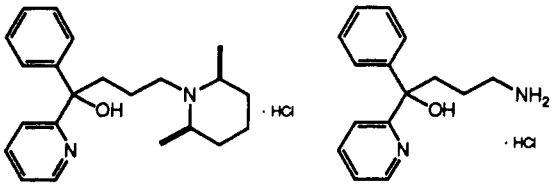
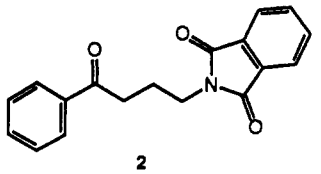
*Received June 4, 1990*

Pirmenol (CI-845) (**1a**) is an antiarrhythmic agent currently in clinical trials.[1] For the synthesis of one of the pirmenol metabolites **1b**, we were unsuccessful in using the Gabriel synthesis[2] to make the primary amine functionality. When we added 2-pyridyllithium to phthalimide **2**, no addition product was isolated. Alternative Gabriel reagents have been developed, but they too have potential drawbacks. They are either amide,[3a,b] phosporamidate,[3c] or sulfonamide[3d,e] derivatives that may interfere with organolithium reagents, or they are reagents[3e,f] requiring undesirable reaction conditions.

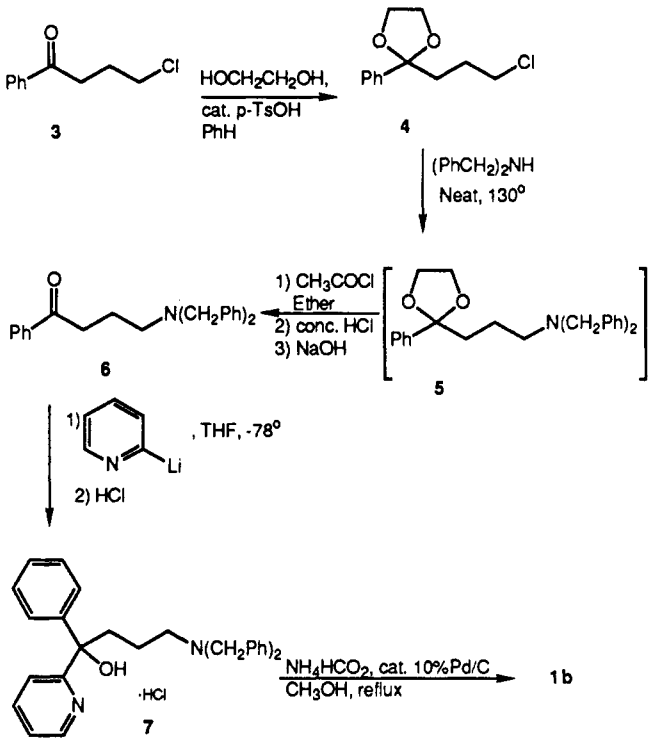


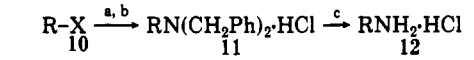

However, we found the dibenzylamino derivative[4] **6** was well suited to our needs. It was easily made using standard conditions, it did not interfere with the 2-pyridyllithium addition, and the dibenzyl groups were easily removed by catalytic transfer hydrogenation (CAT)[5] using ammonium formate in methanol and 10% Pd/C as catalyst.

The synthesis of **1b** is outlined in Scheme I. It was necessary to protect the ketone **3** after two alternate routes failed. The shortest route would have been the addition of 2-pyridyllithium directly to **3**, followed by the use of standard Gabriel chemistry to introduce the primary amino group. However the major product of the addition was **8** (52%) and unreacted starting material (20%). Another possible route was the addition of dibenzylamine to **3**, thereby giving **6** directly. However, experience with the synthesis of pirmenol indicated the major product from this reaction was likely to be cyclopropyl phenyl ketone **9**. Therefore the ketone was protected as the ketal **4**.

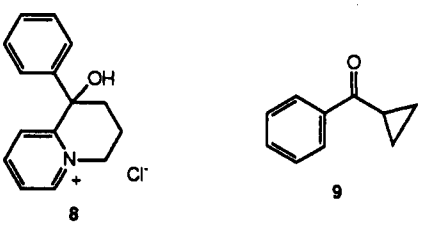
**Scheme I. Preparation of Pirmenol Metabolite 1b**




**Scheme II.[a] General Preparation of Primary Amines[b]**




[a] (a) $(PhCH_2)_2NH$, $K_2CO_3$, diglyme, 140 °C; (b) HCl(g), 2-propanol; (c) $NH_4HCO_2$, cat. 10% Pd/C, $CH_3OH$, 65 °C. [b] The reaction conditions used to prepare **1b** were different as described.




High yields were sacrificed for product purity in the ketal formation step (**3** → **4**; 48%) and the 2-pyridyllithium addition step (**6** → **7**; 63%). Nevertheless the overall yield for the five steps was 16%. The high yields obtained for the dibenzylamine addition (**4** → **5**; >85%) and the CAT hydrogenolysis (**7** → **1b**; 63%) encouraged us to investigate this method as an alternative to the Gabriel synthesis.

We set about to convert some simple alkyl halides into primary amines (Scheme II). Examples of these conversions are listed in Table I. The yields of the free bases of **11a-e** were generally in the 85-95% range except for the hindered bromide **10b** (48%). Also, the HCl salt **11b** was difficult to crystallize in good yield, which resulted in the low overall yield for the conversion. However the

(1) See: A Symposium: Pirmenol-A Unique, New Antiarrhythmic Agent. Just, H., Ed. *Am. J. Card.* **1987**, *59*(16), 1H.
(2) (a) Gabriel, S. *Ber. Dtsch. Chem. Ges.* **1887**, *20*, 2224. (b) Gibson, M. S.; Bradshaw, R. W. *Angew. Chem., Int. Ed. Engl.* **1968**, *7*, 919-930.
(3) (a) Grehn, L.; Ragnarsson, U. *Synthesis* **1987**, 275. (b) Clarke, C. T.; Elliott, D.; Jones, J. H. *J. Chem. Soc., Perkin Trans. 1* **1978**, 1088. (c) Zwierzak, A.; Pillchowska, S. *Synthesis* **1982**, 922. (d) Hendrickson, J. B.; Bergeron, R.; Giga, A.; Sternbach, D. D. *J. Am. Chem. Soc.* **1973**, *95*, 3412. (e) Hendrickson, J. B.; Bergeron, R.; Sternbach, D. D. *Tetrahedron* **1975**, *31*, 2517. (f) Mukaiyama, T.; Tsuji, T.; Watanabe, Y. *Chem. Lett.* **1978**, 1057.
(4) Only two examples of the synthesis of primary amines by *N,N*-didebenzylation have been reported. See: (a) Pawlowski, M.; Grczyca, M. *Pol. J. Chem.* **1981**, *55*(4), 837-41. (Engl.). (b) La Manna, A.; et al. *Farmaco, Ed. Sci.* **1967**, *22*, 667.
(5) For a review, see: Johnstone, R.; Wilby, A. *Chem. Rev.* **1985**, *85*, 129-70.
(6) Brown, H. C.; Kim, K. W.; Screbnik, M.; Singaram, B. *Tetrahedron* **1987**, *43*(18), 4071.
(7) Koziara, A.; Osowska-Pacewicka, K.; Zawadzski, S.; Zwierzak, A. *Synthesis* **1985**, 202.

0022-3263/91/1956-0457$02.50/0 