separated, and the organic layer was washed with 2 × 500 mL of water and 500 mL of brine. The combined aqueous layers were reextracted with EtOAc/CH_2Cl_2 (2:1) and discarded. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated in vacuo to give 79 g of the title compound as a light tan colored solid, mp 153–155 °C: $[\alpha]_D$ = −73.73° (c 1.58, $CHCl_3$); DCI MS 410 $(M + H)^+$; ^1H NMR (300 MHz, $CDCl_3$) δ 1.5–2.05 (m, 25 H), 2.54 (dd, 1 H, J = 16.0, 4.0 Hz), 2.62 (dd, 1 H, J = 16.0, 11.0 Hz), 2.91 (dd, 1 H, J = 13.5, 6.5 Hz), 3.12 (dd, 1 H, J = 10.0, 4.0 Hz), 3.20 (dd, 1 H, J = 13.5, 3.0 Hz), 4.59 (m, 1 H), 6.49 (d, 1 H, J = 7.0 Hz), 6.60 (d, 1 H, J = 7.0 Hz). Anal. Calcd for $C_{26}H_{35}NO_3$: C, 76.25; H, 8.61; N, 3.42. Found: C, 76.36; H, 8.57; N, 3.33.

(1*R*,3*S*)-3-Adamantyl-1-(aminomethyl)-3,4-dihydro-5,6-dihydroxy-1*H*-2-benzopyran Hydrochloride (−)-1. A solution of anhydrous HCl in DME (900 mL of a 5 N solution) and 9 mL of H_2O was added to amine 18 (74 g, 0.181 mol), and the reaction mixture was heated at reflux temperature for 3 h. The reaction mixture was concentrated in vacuo, the residue was dissolved in ethanol (350 mL), and the product was triturated with ether (2 L). The precipitate was washed with ether and dried and then recrystallized from ethanol/ether to afford 53 g (80%) as colorless crystals, mp 220 °C: $[\alpha]_D$ = −69.4° (c 1.1, MeOH); DCI MS 330 $(M + H)^+$; ^1H NMR (300 MHz, CD_3OD) δ 1.65–2.05 (m, 15 H), 2.6 (dd, 1 H, J = 16.5, 12.0 Hz), 2.72 (dd, 1 H, J = 16.5, 3.0 Hz), 3.08 (dd, 1 H, J = 12.6, 7.5 Hz), 3.15 (dd, 1 H, J = 12.0, 3.0 Hz), 3.54 (dd, 1 H, J = 12.6, 3.2 Hz), 4.85 (m, 1 H), 6.5 (d, 1 H, J = 8.4 Hz), 6.69 (d, 1 H, J = 8.4 Hz). Anal. Calcd for $C_{20}H_{22}ClNO_3$ + 0.6 EtOH: C, 64.70; H, 8.09; N, 3.56. Found: C, 64.37; H, 7.81; N, 3.63.

HPLC Separations. Bromohydrin 15 was analyzed as the corresponding naphthoate ester prepared using 1-naphthoyl chloride and DMAP in CH_2Cl_2. The HPLC sample was prepared by preparative TLC (50- × 100- × 0.25-mm plate, 10% hexane/ethyl acetate eluant). The samples were analyzed on a Chiracel OD column using the following parameters: mobile phase, 98% hexane/2-isopropanol with 0.1% diethylamine; flow rate, 0.5 mL/min; UV detection (λ = 293 nM).

Alcohol 5 was analyzed without derivatization using the Chiralcel OD column with the following parameters: mobile phase, 98% hexane/2-propanol with 0.1% diethylamine; flow rate 0.5 mL/min; UV detection (λ = 280 nM).

Compound 1 was analyzed by standard HPLC by the Mosher amide method.[10] The amides were prepared using excess (*S*)-(−)-α-methoxy-α-(trifluoromethyl)phenylacetic acid chloride and DMAP in DMF to ensure complete reaction. Without purification, the amides were injected on a C18 Rainin axial compression column under the following conditions: mobile phase, 30:70 (v/v) A:B (A = 0.01 M aqueous ammonium perchlorate, 0.1% trifluoroacetic acid, B = 25% methanol/acetonitrile); flow rate 1.5 mL/min; UV detection (λ = 275 nM).

Acknowledgment. We would like to thank Dr. Stephen Spanton of the Abbott Analytical Department for the X-ray crystallographic structure determination of compound (−)-1.

Enantioselective Construction of Natural (+)-Pallescensin A. A Sigmatropic Pathway to Furanosesquiterpenes

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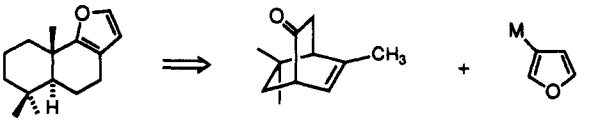
Received August 25, 1992

Addition of the cerium reagent derived from 3-lithiofuran and anhydrous $CeCl_3$ to optically pure bicyclic ketone 2 affords alcohol 4 selectively. Anionic oxy-Cope rearrangement of 4 in hot diglyme results in conversion to keto aldehyde 6, a consequence of β-elimination following upon the [3,3]sigmatropic event. Advantage was then taken of chemoselective acetalization and unidirectional introduction of an enone double bond. Regio- and stereoselective epoxidation of 8 was a prelude to formation of the furan ring by BF_3-etherate-promoted cyclization. Once the carbonyl group was reduced with alane, catalytic hydrogenation in the presence of diethylamine gave the title compound. An alternative scheme involving silylation of the furan ring as a protective maneuver, while entirely workable, was both less direct and less efficient.

Notwithstanding the extensive use that has been made of the anionic oxy-Cope rearrangement in natural product total synthesis,[1] the adaptation of furan derivatives to the convergent variant of this [3,3] sigmatropic process has been reported only once.[2] The ready availability of many functionalized furans[3] and the richness of the furanosesqui- and diterpene field[4] appeared to us to be factors well suited to amalgamation. The resulting initial thrust is exemplified herein by an enantioselective route to (+)-pallescensin A (1).



1 2 3

This marine metabolite was first isolated in 1975 from the sponge *Disidera pallescens* by Cimino and co-workers.[5] In the intervening years, 1 has been prepared on several occasions as either a racemate[6] or a pure enantiomer.[7,8]

(1) (a) Paquette, L. A. *Synlett* **1990**, 67. (b) Paquette, L. A. *Angew. Chem.* **1990**, *102*, 642; *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 609.

(2) Jung, M. E.; Hudspeth, J. P. *J. Am. Chem. Soc.* **1978**, *100*, 4309.

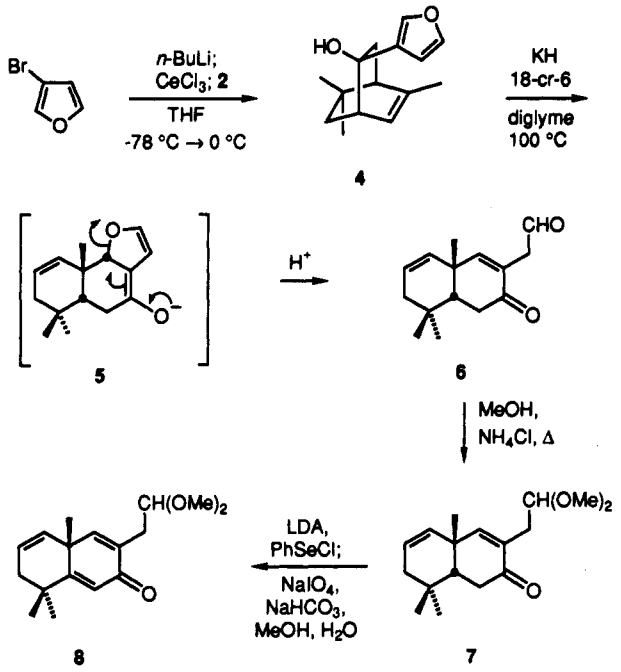
(3) (a) Dean, F. M. In *Advances in Heterocyclic Chemistry*; Katritzky, A. R., Ed.; Pergamon Press: New York, 1982; Vol. 30, p 167. (b) Dean, F. M. In *Advances in Heterocyclic Chemistry*; Katritzky, A. R., Ed.; Pergamon Press: New York, 1982; Vol. 31, p 237. (c) Dean, F. M.; Seargent, M. V. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Bird, C. W., Cheeseman, G. W. H., Eds.; Pergamon Press: New York, 1984; Vol. 4, p 599. (d) Donnely, D. M. X.; Meegan, M. J. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Bird, C. W., Cheeseman, G. W. H., Eds.; Pergamon Press: New York, 1984; Vol. 4, p 657.

(4) Padwa, A.; Ishida, M. *Tetrahedron Lett.* **1991**, *32*, 5673 and relevant references cited therein.

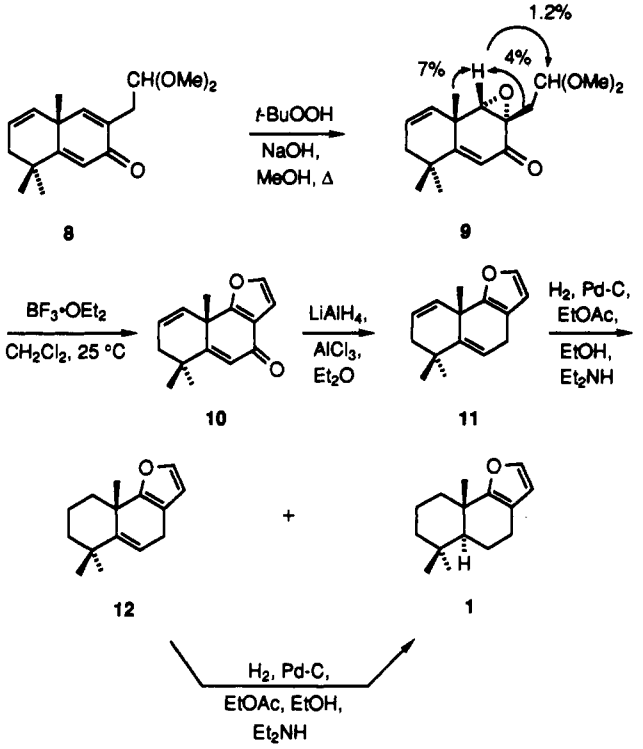
(5) Cimino, G.; De Stefano, S.; Guerriero, A.; Minale, L. *Tetrahedron Lett.* **1975**, 1417, 1425.

0022-3263/92/1957-7118$03.00/0

Scheme I



Scheme II



The absolute configuration of natural (+)-pallescensin A, shown in **1**, is known from the work of Matsumoto and Usui.[8]

In contemplating a synthesis of **1** based on the oxy-Cope stratagem, we viewed the known optically active ketone **2**,[9] $[\alpha]_D$ −497° (*c* 4.58, $CHCl_3$), 100% ee, to be sufficiently accessible to serve as starting material. Also favored was an organometallic reagent **3** derived from commercially available 3-bromofuran. Our purposes were best served by halogen–metal exchange with *n*-butyllithium at −78 °C followed by conversion to the dichlorocerate.[10] Under these conditions, enolization was not a complication and the facial selectivity of nucleophilic attack at the carbonyl carbon was appropriately high.[11]

Following arrival at **4** (Scheme I), KH and 18-crown-6 were employed to promote the structural isomerization. Notwithstanding the favorable kinetic acceleration anticipated from these reaction conditions, elevated temperatures were necessary to accomplish the desired transformation. Our operating assumption is that the need to adopt a boatlike transition state conformation and the somewhat enhanced resonance stabilization of the furan ring combine to serve as deterrents to the isomerization. The preferred solvent was either THF (sealed tube) or diglyme at 100 °C.[12] In either case, the conversion to enolate anion **5** was followed by in situ β-elimination of the alkoxide ion. The formation of an enolate in the ring-cleaved product is envisioned to be the driving force that facilitates the operation of this retro-Michael step.

Heating **6** with NH_4Cl in methanol,[13] the method of choice for chemoselective acetalization, gave **7** in 90% yield. With introduction of the third double bond as in **8**,[14] several objectives had been met. A decalone containing all of the necessary carbon atoms had been made available in four steps. The lone stereogenic center in **8** was of the proper absolute configuration for ultimate conversion to (+)-**1**. Also, the angular methyl group constituted a stereocontrol element well suited to uncomplicated introduction of the requisite trans ring fusion.

From the practical standpoint, **8** did not respond in desirable fashion to dissolving metal[15] or conjugate hydride reduction.[16] Catalytic hydrogenation at this stage also gave rise to unsatisfactory levels of regio- and stereoselectivity. Recourse was soon made instead to regioselective epoxidation with alkaline *tert*-butyl hydroperoxide.[17] That entry of the oxirane oxygen had occurred exclusively from the α-face to give **9** (79%) was strongly supported

(6) (a) Tanis, S. P.; Herrinton, P. M. *J. Org. Chem.* **1983**, *48*, 4572. (b) Nasipuri, D.; Das, G. *J. Chem. Soc., Perkin Trans. 1* **1979**, 2776.

(7) (a) Shishido, K.; Umimoto, K.; Shibuya, M. *Heterocycles* **1990**, *31*, 597. (b) Smith, A. B., III; Mewshaw, R. *J. Org. Chem.* **1984**, *49*, 3685. (c) Akita, T.; Oishi, T. *Chem. Pharm. Bull.* **1981**, *29*, 1580.

(8) Matsumoto, T.; Usui, S. *Chem. Lett.* **1978**, 105.

(9) Maleczka, R. E., Jr.; Paquette, L. A. *J. Org. Chem.* **1991**, *56*, 6538.

(10) (a) Imamoto, T.; Sugiura, Y.; Takiyama, N. *Tetrahedron Lett.* **1984**, *25*, 4233. (b) Imamoto, T.; Sugiura, Y. *J. Organomet. Chem.* **1985**, *285*, C21. (c) Imamoto, T.; Takiyama, N.; Nakamura, K. *Tetrahedron Lett.* **1985**, *26*, 4763.

(11) Two minor byproducts were occasionally observed (less than 5% if seen). These were **i** resulting from approach of the nucleophile from the more sterically hindered π-surface or **ii** resulting from the incomplete consumption of *n*-BuLi during the halogen–metal exchange:

i ii

(12) Heating **4** to 120 °C in *N*-methylpyrrolidinone [Utagawa, A.; Hirota, H.; Ohno, S.; Takahashi, T. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 1207] resulted in dehydration followed either by retro-Diels–Alder fragmentation to give **iii** or 1,3-prototropic shift to give **iv**:

iii iv

(13) DeGraw, J. I.; Goodman, L.; Baker, B. R. *J. Org. Chem.* **1961**, *26*, 1156.

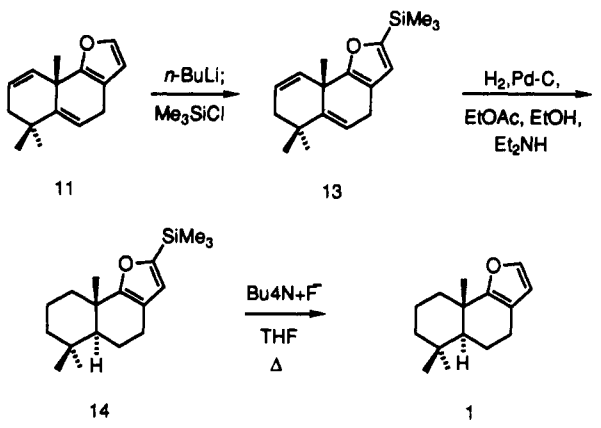
(14) Reich, H. J.; Renga, J. M.; Reich, I. L. *J. Am. Chem. Soc.* **1975**, *97*, 5434.

(15) Pradhan, S. K. *Tetrahedron* **1986**, *42*, 6351.

(16) Tsuda, T.; Satomi, H.; Hayashi, T.; Saegusa, T. *J. Org. Chem.* **1987**, *52*, 439.

(17) Wasson, R. L.; House, H. O. *Organic Syntheses*; Wiley: New York, 1963; Collect. Vol. IV, p 552.

Scheme III



by NOE studies (Scheme II). In light of subsequent findings that attempted saturation of **9** by hydrogenation under heteroatom-directing conditions[18,19] led to its destruction, the furan ring was next elaborated by cyclization of **9** with boron trifluoride etherate in CH_2Cl_2 at 25 °C.[20] The direct acquisition of **10** in this manner was exploited by ensuing reductive removal of the carbonyl oxygen with alane.[21] The enantiomeric purity of (+)-**10** was established as 100% ee by NMR studies involving the use of $Eu(dcm)_3$ as chiral shift reagent. Whereas (±)-**10** exhibited twin peaks of equal intensity in $CDCl_3$ at δ 6.90 and 6.87, the dextrorotatory sample showed only a single absorption at δ 6.87.

We next surveyed the possibility of transforming **11** into **1** by two different means. The more direct pathway involved hydrogenation over 5% palladium on carbon at 1 Torr in a solvent system composed of ethyl acetate, ethanol, and diethylamine[22] (ratio 1:1:0.2). In order to skirt overreduction, the progress of the reaction was arrested when the **12**:**1** ratio was approximately 1:1. Beyond this conversion level, dihydro-**1** began to make its appearance (GC-MS analysis). Following product separation on silica gel impregnated with silver nitrate (5%),[23] **12** was recycled for added production of the target compound.

The second option, exercised on racemic **11**, avoids the need for chromatography and monitoring of the extent of hydrogenation. Introduction of a trimethylsilyl substituent onto the furan ring as in **13** (Scheme III) was expected to retard saturation of the heterocyclic ring sufficiently to be considered a protecting group.[24] Indeed, the conversion of **14** proved uneventful. Desilylation of **14** with tetra-*n*-butylammonium fluoride in THF provided (±)-**1**. Although this sequence is eminently workable, the overall yield is lower than that realized by direct passage via **12**.

The synthetic (+)-pallescensin A exhibited spectroscopic data (IR, ^1H NMR) identical to that previously reported. Its ^{13}C NMR spectrum, recorded in $CDCl_3$ solution, consists of 14 clearly defined lines; the signal appearing at 35.6 ppm is due to two carbons. The optical rotation of our sample, $[\alpha]^{25}_D$ +78.8° (*c* 1.24, $CHCl_3$), compares favorably with values previously cited: $[\alpha]^{22}_D$ +60.4° (*c* 0.9, $CHCl_3$);[7c,8] $[\alpha]^{24}_D$ +81.3° (*c* 1.3, $CHCl_3$);[7b] $[\alpha]_D$ +78.2° (*c* 1.24, $CHCl_3$).[7a]

In summary, the present study has established the feasibility of preparing (+)-pallescensin A in an enantiocontrolled manner via anionic oxy-Cope technology starting from the readily available bicyclic ketone **2** and 3-bromofuran.

Experimental Section

General Experimental Data. See ref 9 for details.

(1*S*,2*R*,4*R*)-2-(3-Furyl)-5,8,8-trimethylbicyclo[2.2.2]oct-5-en-2-ol (4). A cold (−78 °C), magnetically stirred solution of *n*-butyllithium in hexanes (8.9 mL of 1 M, 8.9 mmol) was treated dropwise under N_2 with 3-bromofuran (1.07 g, 7.28 mmol) dissolved in dry THF (20 mL). After 10 min, this mixture was added via cannula to a cold (−78 °C), magnetically stirred suspension of anhydrous $CeCl_3$ [from 3.6 g (9.66 mmol) of the heptahydrate dried at 130 °C and 0.1 Torr for 8 h and stirred for 1 h in the THF]. After this mixture had been stirred for 3 h at −78 °C, ketone **2** (398 mg, 2.43 mmol) in THF (1 mL) was introduced, stirring was maintained at −78 °C for 1 h, and warming to 25 °C was allowed to proceed slowly. After cooling to 0 °C, quenching was accomplished through addition of saturated NH_4Cl solution (40 mL). The product was extracted into ether (3 × 40 mL) and the combined organic layers were dried and evaporated. Chromatography of the residue on silica gel (elution with 10% ether in petroleum ether) gave **4** (502 mg, 89%) as a faintly yellow solid: mp 86–87 °C; IR ($CHCl_3$, cm^{-1}) 3620–3540; ^1H NMR (300 MHz, C_6D_6) δ 7.13 (m, 2 H), 6.28 (s, 1 H), 5.59 (dt, *J* = 6.5, 1.4 Hz, 1 H), 2.39 (m, 1 H), 2.18 (dd, *J* = 12.6, 2.3 Hz, 1 H), 2.10 (dd, *J* = 13.9, 2.4 Hz, 1 H), 1.72 (m, 1 H), 1.68 (d, *J* = 1.5 Hz, 3 H), 1.63–1.57 (m, 2 H), 1.29 (s, 3 H), 1.01 (m, 1 H), 0.90 (s, 3 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 143.9, 142.8, 138.3, 136.7, 124.0, 109.7, 72.2, 49.2, 44.7, 39.2, 35.8, 32.5, 32.0, 28.3, 21.8; MS *m*/*z* (M^+) calcd 232.1463, obsd 232.1486; $[\alpha]^{25}_D$ −84.7° (*c* 7.12, $CHCl_3$).

Anal. Calcd for $C_{15}H_{20}O_2$: C, 77.55; H, 8.68. Found: C, 77.24; H, 8.81.

(4a*R*,8a*R*)-3,4,4a,5,6,8a-Hexahydro-5,5,8a-trimethyl-3-oxo-2-naphthaleneacetaldehyde (6). To a magnetically stirred slurry of oil-free potassium hydride (358 mg, 8.94 mmol) in anhydrous diglyme (10 mL) was added **4** (415.6 mg, 1.79 mmol) dissolved in the same medium (20 mL). The mixture was stirred at 25 °C for 15 min, at which time 18-crown-6 (2.36 g, 8.94 mmol) in diglyme (10 mL) was introduced. The contents were heated at 100 °C for 1 h, cooled to −78 °C, and treated with methanol (10 mL) followed by saturated NH_4Cl solution (10 mL). After dilution with ether (40 mL), the mixture was washed with brine, and the organic phase was dried and concentrated first under house vacuum, and then under 0.1 Torr at 30 °C to remove the diglyme. The residue was purified by silica gel chromatography (elution with 50% ether in petroleum ether) to give 301.3 mg (73%) of **6** as a colorless oil; IR ($CHCl_3$, cm^{-1}) 1712, 1663; ^1H NMR (300 MHz, $CDCl_3$) δ 9.54 (t, *J* = 1.8 Hz, 1 H), 6.33 (s, 1 H), 5.62 (m, 1 H), 5.37 (dd, *J* = 9.7, 2.1 Hz, 1 H), 3.12 (dt, *J* = 4.7, 1.0 Hz, 1 H), 2.67 (m, 2 H), 1.93–1.79 (m, 2 H), 1.66 (dd, *J* = 17.4, 5.9 Hz, 1 H), 1.39–1.09 (m, 1 H), 1.24 (s, 3 H), 0.93 (s, 3 H), 0.67 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 198.5, 197.8, 154.0, 131.9, 128.7, 125.5, 49.5, 44.0, 40.4, 37.9, 34.8, 32.8, 29.3, 28.9, 23.8; MS *m*/*z* (M^+) calcd 232.1463, obsd 232.1473; $[\alpha]^{25}_D$ +48.5° (*c* 3.07, $CHCl_3$).

Anal. Calcd for $C_{15}H_{20}O_2$: C, 77.55; H, 8.68. Found: C, 77.28; H, 8.69.

(4a*R*,8a*R*)-3,4,4a,5,6,8a-Hexahydro-5,5,8a-trimethyl-3-oxo-2-naphthaleneacetaldehyde 2-(Dimethyl acetal) (7). Aldehyde **6** (301.3 mg, 1.30 mmol) and ammonium chloride (50 mg) were stirred in refluxing methanol (25 mL) for 2 h. The reaction mixture was cooled, evaporated, taken up in ether, and eluted through a pad of silica to give 325.3 mg (90%) of **7** as a faint yellow oil: IR ($CHCl_3$, cm^{-1}) 1669; ^1H NMR (300 MHz, C_6D_6) δ 6.08 (s, 1 H), 5.45 (m, 1 H), 5.20 (dd, *J* = 10.0, 2.7 Hz, 1 H), 4.65 (dd, *J* = 6.3, 5.2 Hz, 1 H), 3.17 (s, 3 H), 3.13 (s, 3 H), 2.71 (dd, *J* = 13.7, 5.1 Hz, 1 H), 2.62 (dd, *J* = 17.5, 1.7 Hz, 1 H), 2.53–2.41

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(22) Bel'skii, I. F.; Shuikin, N. I. *Russ. Chem. Rev.* **1963**, *32*, 307. Failure to include the diethylamine resulted in overhydrogenation and loss of stereoselectivity.

(23) Cagniant, D. *Complexation Chromatography*; Marcel Dekker: New York, 1972; p 149.

(24) Corey, E. J.; Xiang, Y. B. *Tetrahedron Lett.* **1987**, *28*, 5403.

(series of m, 2 H), 1.67 (d, J = 17.3 Hz, 1 H), 1.57 (d, J = 6.8 Hz, 1 H), 1.45 (dd, J = 17.1, 5.8 Hz, 1 H), 0.96 (s, 3 H), 0.76 (s, 3 H), 0.74 (s, 3 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 197.2, 151.8, 133.1, 132.1, 124.9, 103.3, 52.8, 52.5, 49.7, 40.9, 37.8, 35.5, 33.9, 32.9, 29.4, 28.9, 23.8; MS m/z (M^+) calcd 278.1882, obsd 278.1890; $[\alpha]^{25}_D$ +44.8° (c 3.23, $CHCl_3$).

Anal. Calcd for $C_{17}H_{26}O_3$: C, 73.35; H, 9.41. Found: C, 73.11; H, 9.32.

(*R*)-3,5,6,8a-Tetrahydro-5,5,8a-trimethyl-3-oxo-2-naphthaleneacetaldehyde 2-(Dimethyl acetal) (8). To a cold (−78 °C), magnetically stirred solution of LDA [from 0.4 mL (2.86 mmol) of diisopropylamine and 1.86 mL (2.60 mmol) of 1.4 M n-butyllithium in hexanes] in anhydrous THF (12 mL) was added **7** (308.8 mg, 1.11 mmol) dissolved in 4 mL of THF. The reaction mixture was stirred for 40 min at which time phenylselenenyl chloride (548 mg, 2.86 mmol) was introduced. After 60 min at this temperature, the mixture was warmed to 25 °C, stirred for 10 h, cooled to 0 °C, and quenched with saturated NH_4Cl solution. After dilution with ether (20 mL), the organic phase was washed with brine (2 × 20 mL) and the aqueous layers were back-extracted with ether. The combined ethereal solutions were dried and concentrated to leave a residue that was purified by chromatography on silica gel (elution with 25% ether in petroleum ether). There was obtained 306.4 mg (64%) of the selenide, 15.4 mg (5%) of unreacted **7**, and 44.4 mg (14%) of trienone **8**.

For the selenide: IR ($CHCl_3$, cm^{-1}) 1665; ^{1}H (300 MHz, C_6D_6) δ 7.82 (m, 2 H), 7.06–6.98 (m, 3 H), 6.08 (d, J = 0.8 Hz, 1 H), 5.42 (m, 1 H), 5.13 (dd, J = 9.9, 2.8 Hz, 1 H), 4.71 (t, J = 5.7 Hz, 1 H), 4.36 (s, 1 H), 3.24 (s, 3 H), 3.16 (s, 3 H), 2.90 (d, J = 5.7 Hz, 2 H), 2.35 (s, 1 H), 1.69 (d, J = 17.0 Hz, 1 H), 1.40–1.31 (m, 1 H), 1.36 (s, 3 H), 0.76 (s, 3 H), 0.70 (s, 3 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 194.6, 150.6, 135.0 (2 C), 133.9, 132.2, 130.7, 129.4 (2 C), 128.4, 124.0, 103.5, 56.6, 53.2, 53.0, 46.5, 41.0, 37.7, 34.8, 34.6, 31.8, 29.1, 22.0; MS m/z (M^+) calcd 434.1363, obsd 434.1366; $[\alpha]^{25}_D$ −96.7° (c 2.20, $CHCl_3$).

A magnetically stirred solution of the selenide (388 mg, 0.896 mmol) in methanol (25 mL) and water (5 mL) was treated with $NaHCO_3$ (376 mg, 4.48 mmol) and sodium periodate (960 mg, 4.49 mmol). A precipitate formed immediately. After 15 min, the reaction mixture was diluted with ether (50 mL) and the separated organic phase was washed with brine, dried, and evaporated. The residue was subjected to silica gel chromatography (elution with 25% ether in petroleum ether) to give 224 mg (91%) of **8** as a pale yellow oil: IR (CCl_4, cm^{-1}) 1670, 1642; ^{1}H NMR (300 MHz, C_6D_6) δ 6.44 (s, 1 H), 6.32 (s, 1 H), 5.40 (dt, J = 9.7, 3.9 Hz, 1 H), 5.28 (dt, J = 9.7, 1.6 Hz, 1 H), 4.80 (t, J = 5.7 Hz, 1 H), 3.19 (s, 3 H), 3.17 (s, 3 H), 2.83 (dd, J = 5.9, 0.5 Hz, 2 H), 1.63 (m, 2 H), 1.11 (s, 3 H), 0.99 (s, 3 H), 0.86 (s, 3 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 186.3, 169.5, 153.3, 132.0, 130.7, 125.5, 123.7, 103.6, 53.1, 52.9, 43.0, 41.8, 36.7, 33.7, 29.3 (2 C), 28.1; MS m/z (M^+) calcd 276.1725, obsd 276.1719; $[\alpha]^{25}_D$ −1.3° (c 0.87, $CHCl_3$).

Anal. Calcd for $C_{17}H_{24}O_3$: C, 73.88; H, 8.75. Found: C, 73.88; H, 8.80.

(1*S*,2*S*,8a*S*)-1,2-Epoxy-1,2,3,5,6,8a-hexahydro-5,5,8a-trimethyl-3-oxo-2-naphthaleneacetaldehyde 2-(Dimethyl acetal) (9). To a solution of **8** (36 mg, 0.129 mmol) and *tert*-butyl hydroperoxide (0.2 mL of 90%, 1.80 mmol) in methanol (5 mL) at 0 °C was slowly added 0.5 mL (3.0 mmol) of 6 N NaOH over 30 min. The reaction mixture was warmed to 70 °C for 3 h, cooled to rt, stirred overnight, and poured into water (20 mL). After ether extraction (3 × 20 mL), the combined ether phases were washed with brine (20 mL), dried, and evaporated. The residue was chromatographed on silica gel (elution with 10% ether in petroleum ether) to give 30 mg (79%) of **9** as white crystals: mp 61–63 °C; IR ($CHCl_3$, cm^{-1}) 1680; ^{1}H NMR (300 MHz, C_6D_6) δ 5.96 (s, 1 H), 5.55 (ddd, J = 9.8, 5.7, 2.3 Hz, 1 H), 5.38 (dd, J = 9.8, 2.6 Hz, 1 H), 4.81 (dd, J = 7.0, 4.5 Hz, 1 H), 3.34 (s, 1 H), 3.12 (s, 3 H), 3.09 (s, 3 H), 2.94 (dd, J = 14.0, 4.5 Hz, 1 H), 1.83 (dd, J = 14.0, 7.0 Hz, 1 H), 1.77 (dt, J = 17.3, 2.6 Hz, 1 H), 1.51 (ddd, J = 17.1, 5.7, 0.6 Hz, 1 H), 1.10 (s, 3 H), 0.93 (s, 3 H), 0.79 (s, 3 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 196.0, 166.5, 130.2, 126.2, 119.4, 102.1, 66.1, 59.4, 53.5, 52.3, 40.7, 40.1, 36.4, 33.0, 28.5, 28.2, 26.7; MS m/z ($M^+ - OCH_3$) calcd 261.1491, obsd 261.1449; $[\alpha]^{25}_D$ −205.3° (c 2.69, $CHCl_3$).

Anal. Calcd for $C_{17}H_{24}O_4$: C, 69.84; H, 8.27. Found: C, 69.47; H, 8.49.

(*S*)-7,9a-Dihydro-6,6,9a-trimethylnaphtho[1,2-*b*]furan-4-(6*H*)-one (10). To a cold (0 °C), magnetically stirred solution of **9** (60 mg, 0.21 mmol) in CH_2Cl_2 (15 mL) was added dropwise 0.5 mL of boron trifluoride etherate. The ice bath was removed, and the mixture was allowed to warm to 25 °C for 30 min, recooled to 0 °C, and treated slowly with saturated $NaHCO_3$ solution (15 mL). After dilution with ether (25 mL), the organic phase was washed with brine, dried, and concentrated. The residue was chromatographed (silica gel, elution with 5% ether in petroleum ether) to give **10** (24 mg, 51%) as a white solid: mp 122–123 °C (from pentane); IR ($CHCl_3$, cm^{-1}) 1670; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41 (d, J = 2.0 Hz, 1 H), 6.73 (d, J = 2.0 Hz, 1 H), 6.29 (s, 1 H), 6.13 (dt, J = 9.7, 1.6 Hz, 1 H), 5.86 (m, 1 H), 2.26 (ddd, J = 17.2, 4.9, 1.5 Hz, 1 H), 2.10 (m, 1 H), 1.61 (s, 3 H), 1.41 (s, 3 H), 1.30 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 183.0, 170.4, 167.3, 142.9, 127.4, 126.9, 124.2, 118.3, 106.1, 42.5, 42.3, 37.1, 30.7, 29.0, 28.9; MS m/z (M^+) calcd 228.1150, obsd 228.1138; $[\alpha]^{25}_D$ +95.3° (c 1.47, $CHCl_3$).

Anal. Calcd for $C_{15}H_{16}O_2$: C, 78.92; H, 7.06. Found: C, 78.68; H, 7.07.

(*S*)-4,6,7,9a-Tetrahydro-6,6,9a-trimethylnaphtho[1,2-*b*]furan (11). A cold (0 °C) slurry of anhydrous $AlCl_3$ (133 mg, 1.0 mmol) in dry ether (5 mL) was treated with $LiAlH_4$ (19 mg, 0.5 mmol) in three portions. After 15 min at 25 °C, the supernatant was transferred to a new flask and cooled to 0 °C. Ketone **10** (78 mg, 0.344 mmol) dissolved in ether (1 mL) was introduced via cannula, stirred for 2 h at 25 °C, cooled to 0 °C, and quenched with ethyl acetate (5 mL) and then saturated Rochelle's salt solution (5 mL). The separated organic phase was washed with brine (2 × 10 mL), and the combined aqueous solutions were back-extracted with ether. The ethereal layers were dried and evaporated to leave a residue that was purified by chromatography on silica gel (elution with hexanes) to give **11** (64 mg, 87%) as a colorless oil: IR (CCl_4, cm^{-1}) 1550, 1507, 1385, 1378, 1260, 1220, 1166, 1118, 1078, 1039, 1000; ^{1}H NMR (C_6D_6) δ 7.12 (d, J = 1.9 Hz, 1 H), 6.36 (dt, J = 9.9, 1.2 Hz, 1 H), 6.02 (d, J = 1.9 Hz, 1 H), 5.63–5.57 (m, 2 H), 3.00 (dd, J = 20.7, 2.6 Hz, 1 H), 2.89 (dd, J = 20.7, 5.1 Hz, 1 H), 1.88 (dt, J = 17.0, 2.6 Hz, 1 H), 1.76 (ddd, J = 16.9, 5.4, 1.2 Hz, 1 H), 1.50 (s, 3 H), 1.20 (s, 3 H), 1.09 (s, 3 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 156.6, 147.2, 141.0, 131.1, 124.6, 117.9, 113.0, 109.7, 41.7, 39.3, 35.6, 30.7, 39.4 (2 C), 24.7; MS m/z (M^+) calcd 214.1358, obsd 214.1329; $[\alpha]^{25}_D$ +42.1° (c 0.66, $CHCl_3$).

Anal. Calcd for $C_{15}H_{18}O$: C, 84.07; H, 8.47. Found: C, 84.29; H, 8.72.

Hydrogenation of 11. To a solution of **11** (30.0 mg, 0.14 mmol) in ethyl acetate (1 mL), ethanol (1 mL), and diethylamine (0.2 mL) was added 27 mg of 5% Pd on carbon. This stirred mixture was blanketed with hydrogen (1 atm). After 24–48 h (depending on the run), a 50:50 mixture of **12** and **1** was produced (GC-MS analysis). The catalyst was removed by filtration through Celite, and the filtrate was concentrated. The residue was chromatographed on silver nitrate impregnated (5%) silica gel (elution with hexanes) to give 13 mg (42%) of **1** as a colorless oil. An increase in solvent polarity to 50% ether in hexane afforded 14 mg (46%) of **12**, which could be recycled to produce additional **1**.

For **12**: colorless oil; IR ($CHCl_3$, cm^{-1}) 1462, 1387, 1373, 1280, 1160, 1139, 1115, 1037, 892; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25 (d, J = 1.8 Hz, 1 H), 6.16 (d, J = 1.8 Hz, 1 H), 5.72 (t, J = 3.7 Hz, 1 H), 3.10 (d, J = 3.7 Hz, 2 H), 2.20 (m, 1 H), 1.89 (m, 1 H), 1.65–1.50 (m, 3 H), 1.42 (s, 3 H), 1.34 (m, 1 H), 1.23 (s, 3 H), 1.16 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 157.8, 148.0, 140.4, 117.5, 111.4, 109.0, 41.5, 36.92, 36.86, 36.2, 33.2, 29.5, 27.3, 24.5, 18.5; MS m/z (M^+) calcd 216.1514, obsd 216.1522; $[\alpha]^{25}_D$ +24.8° (c 0.92, $CHCl_3$).

For **1**: IR ($CHCl_3$, cm^{-1}) 1500, 1455, 1375; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.18 (d, J = 1.8 Hz, 1 H), 6.11 (d, J = 1.8 Hz, 1 H), 2.52–2.31 (m, 2 H), 2.17–2.08 (m, 1 H), 1.87–1.21 (series of m, 8 H), 1.19 (s, 3 H), 0.94 (s, 3 H), 0.91 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) ppm 159.8, 140.0, 113.7, 110.1, 52.4, 41.9, 35.6 (2 C), 33.4, 33.0, 22.7, 21.4, 21.3, 19.5, 18.6; MS m/z (M^+) calcd 218.1671, obsd 218.1670; $[\alpha]^{25}_D$ +78.8° (c 1.24, $CHCl_3$).

Trimethyl(4,6,7,9a-tetrahydro-6,6,9a-trimethylnaphtho-[1,2-*b*]furan-2-yl)silane (13). A cold (−20 °C), magnetically stirred solution of (±)-**11** (46 mg, 0.215 mmol) in dry THF (15 mL) was treated with n-butyllithium (2.3 mL of 1.4 M in hexanes, 3.22 mmol), stirred for 4 h at this temperature, and cooled to −78

°C prior to the addition of a premixed solution of chlorotrimethylsilane (0.8 mL, 6.5 mmol) and triethylamine (1.4 mL, 9.75 mmol) in THF (5 mL). The reaction mixture was stirred at -78 °C for 60 min, allowed to warm slowly to 25 °C over 12 h, recooled to 0 °C, and quenched with saturated NH_4Cl solution (20 mL). Following dilution with ether (20 mL), the organic phase was washed with brine (2 × 10 mL) and the combined aqueous layers were extracted with ether. The ethereal solutions were dried and evaporated to leave a residue, which was chromatographed on silica gel (elution with hexanes) to give 46 mg (75%) of **13** as a clear colorless oil: IR (CCl_4, cm^{-1}) 1605, 1495, 1387, 1368, 1255, 1115, 1087, 1046, 1012, 946, 850; ^1H NMR (300 MHz, C_6D_6) δ 6.44 (m, 1 H), 6.41 (s, 1 H), 5.66 (m, 1 H), 5.62 (m, 1 H), 3.07 (dd, J = 20.6, 2.5 Hz, 1 H), 2.97 (dd, J = 20.6, 5.1 Hz, 1 H), 1.88 (dt, J = 16.9, 2.5 Hz, 1 H), 1.7 (ddd, J = 16.9, 5.4, 1.2 Hz, 1 H), 1.53 (s, 3 H), 1.21 (s, 3 H), 1.11 (s, 3 H), 0.26 (s, 9 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 161.0, 158.2, 147.4, 131.2, 124.6, 120.4, 118.1, 113.4, 41.7, 39.8, 35.6, 30.8, 29.41, 29.37, 24.7, -1.3 (3 C); MS m/z (M^+) calcd 286.1753; obsd 286.1722.

Anal. Calcd for $C_{18}H_{26}OSi$: C, 75.46; H, 9.15. Found: C, 75.01; H, 9.08.

Trimethyl(*trans*-4,5,5a,6,7,8,9,9a-octahydro-6,6,9a-trimethylnaphtho[1,2-*b*]furan-2-yl)silane (14). The hydrogenation of **13** (30 mg, 0.105 mmol) was affected as before except that an additional 30 mg of 5% Pd/C was added after 48 h and reduction was allowed to proceed for an additional day. Comparable workup furnished 21 mg (68%) of **14** as a colorless oil: IR ($CHCl_3$, cm^{-1}) 1460, 1382, 1303, 1122; ^1H NMR (300 MHz, $CDCl_3$) δ 6.37 (s, 1 H), 2.52-2.32 (m, 2 H), 1.82 (dd, J = 13.2, 6.4 Hz, 1 H), 1.72 (dt, J = 13.7, 3.4 Hz, 1 H), 1.59-1.21 (series of m, 7 H), 1.19 (s, 3 H), 0.93 (s, 3 H), 0.91 (s, 3 H), 0.21 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) ppm 164.3, 157.4, 120.3, 113.8, 52.4, 42.0, 36.9, 35.4, 33.5, 33.0, 22.6, 21.2, 19.6, 18.6, -1.5 (3 C); MS m/z (M^+) calcd 290.2066, obsd 290.2071.

Anal. Calcd for $C_{18}H_{30}OSi$: C, 74.42; H, 10.41. Found: C, 74.39; H, 10.51.

Desilylation of 14. To a solution of **14** (11 mg, 0.037 mmol) in THF (1 mL) was added 1 mL of 1 M tetra-*n*-butylammonium fluoride solution in THF, and the mixture was stirred at reflux for 8 h, cooled, and diluted with ether (5 mL) prior to washing with brine (2 × 5 mL). The organic phase was dried and concentrated to leave a residue that was chromatographed on silica gel (elution with hexanes). There was obtained 5 mg (66%) of racemic **1**.

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A Rapid, Convergent, and Regioselective Synthesis of Anthracenes

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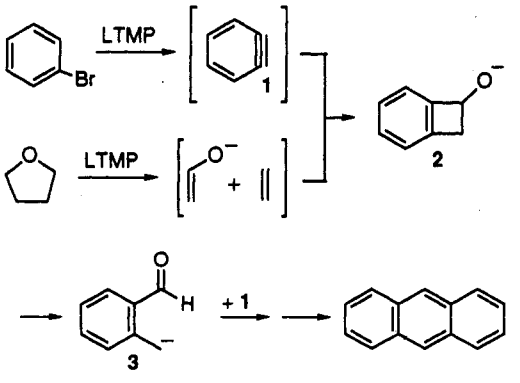
Anthracenes are obtained in moderate to good yield by the simultaneous treatment of benzocyclobutenols and halobenzenes with LTMP in tetrahydropyran. In the key step of this one-pot process, *o*-toluoyl anion intermediates from the known ring-opening of benzocyclobutenoxides add to halobenzene derived arynes. Methoxy-substituted benzocyclobutenols which are readily made regiospecifically by known methods also react regiospecifically with the single benzyne generated from either a 2- or 3-haloanisole. For example, the only trimethoxyanthracene isolated (48% yield) from the reaction of 6-methoxybenzocyclobutenol (**8**) with 5-chloro-1,3-dimethoxybenzene is the 1,3,8-isomer **20**. When 1,2-dihydrocyclobuta[*l*]phenanthren-1-ol (**14**) and/or halonaphthalenes are the reactants, benzannulated anthracenes are formed; e.g., tribenz[*a*,*c*,*h*]anthracene in 68% yield from **14** and bromonaphthalene. In another extension, pentaphene (**31**) was made in one pot from *o*-dichlorobenzene.

As part of a study on O-demethylation, we recently wanted several methoxyanthracenes. However, an examination of the literature indicated that the most desired compounds either were unknown or available only by multistep routes although related anthraquinones have received much attention as dye precursors and recently as anticancer agents. In the search for methodology for adaptation, the Fleming-Mah[1] synthesis of anthracene by treatment of bromobenzene with lithium 2,2,6,6-tetramethylpiperidide (LTMP) in refluxing THF was noted. In this process, an intermediate benzyne (**1**) reacts with acetaldehyde enolate (from metalation-fragmentation of THF by LTMP) to give benzocyclobutenoxide (**2**). This tautomerizes to the *o*-toluoyl anion **3** which adds to more **1** (two step anionic or [4 + 2] electrocyclic process) to produce anthracene after dehydration.



The success of the reaction depends on the fact that LTMP is an extremely poor trap for benzynes.[2] It is also important that **3** is generated in the absence of its conjugate acid and thus is not trapped in a self aldol condensation. Finally it is known that both *o*- and *m*-haloanisoles are converted to *o*-benzynes with bases and that the latter react with nucleophiles entirely at the 3-position.[3] Thus,

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