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Sulfenium Ion Promoted Polyene Cyclizations in Natural Product Synthesis. An Efficient Biomimetic-like Synthesis of (±) Nimbidiol

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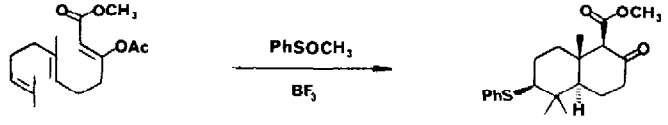
Abstract. A four step synthesis of the modified diterpene (±) nimbidiol (**3**) from (3,4-dimethoxyphenyl)acetonitrile is described which relies on a sulfenium ion promoted polyene cyclization. A key feature of this synthesis is the one flask reductive desulfurization-oxidative decyanation sequence used to convert the post cyclization intermediates **9a,b** into prenimbidiol **10**.

Cationic polyene cyclizations initiated by allylic carbonium ions[1] and mercuronium ions[2a-c] have been utilized extensively for the elaboration of polycyclic ring systems. Despite the interest which has recently been shown in the latter method for initiating polycycle annulation, several limitations hinder the general application of mercuronium ion based strategies to problems of synthetic interest.[3] Recently, we reported the first examples of polyene cascade cyclizations (e.g., **1** → **2**) promoted by sulfenium ions.[4] In this letter we wish to provide the experimental details of this new method in the context of its application to a concise stereospecific synthesis of (±) nimbidiol (**3**).



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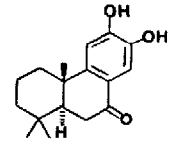

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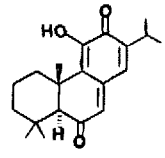

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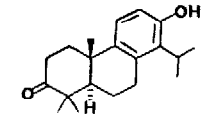

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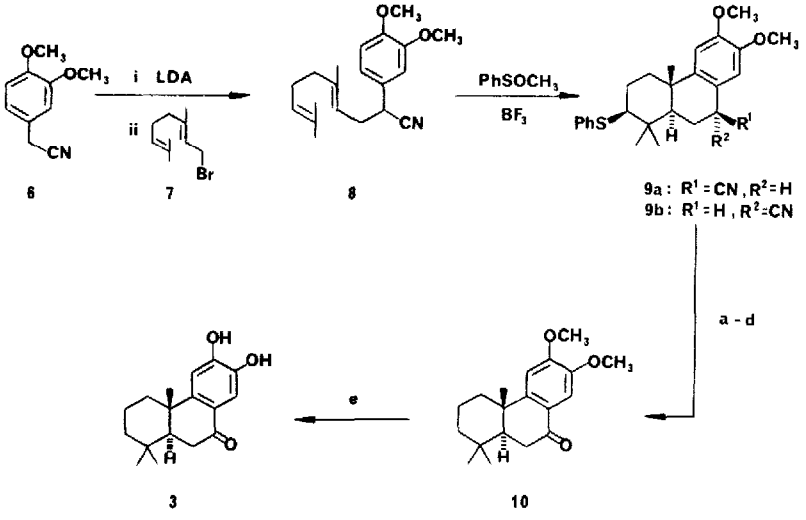
The modified diterpenoid (+) nimbidiol (**3**) was recently isolated from the root bark of Azadirachta indica.[5] The relatively simple phenanthrenoid skeleton of **3** suggested that it might serve as a prototype for the synthesis of the more complicated diterpenes (±) taxodione (**4**) and (±) totarolone (**5**). A stereospecific four step synthesis of (±) nimbidiol (**3**) from commercially available starting materials via a sulfenium ion promoted cascade annulation is described below. Lithiation of (3,4-dimethoxyphenyl)acetonitrile (**6**) (1.00 equiv. LDA, THF, -78 °C) followed by alkylation with (E)-1-bromo-3,7-dimethylocta-2,6-diene (**7**) (1.0 equiv., -78 °C → 25 °C) furnished the unsaturated nitrile **8** in 67% yield after chromatography. The sulfenylative cyclization of **8** was smoothly effected by its addition to a preformed mixture of methyl benzenesulfenate (1.05 equiv.) and BF_3 (2.10 equiv.) in CH_3NO_2 maintained at -30 °C to give the octahydrophenanthrenes **9a** and **9b** (**9a**/**9b** = 1) in 85% isolated yield.[6,7] Several prospective reaction sequences for the conversion of the epimeric nitriles **9a,b** to the benzodecalone **10** were then evaluated. In this connection it is noteworthy that efforts to selectively excise the phenylthio moiety from **9a,b** with W2 Raney nickel or lithium amalgam[8] led to partial reductive cleavage of the benzylic cyano substituent. It was ultimately determined that the transformation of **9a,b** to **10** could be accomplished in one operation by initially protecting the nitrile function as its lithio derivative. Accordingly, lithiation of the benzylic position of **9a,b** [$LiN(SiMe_3)_2$, 1.5 equiv.] followed by reductive desulfurization using lithium naphthalenide (6.8 equiv.) at 0 °C and final oxidative decyanation [a., O_2(-78 °C), b., $SnCl_2$-HCl(aq.), 0 °C][9] provided the ketone **10** in 94% overall yield. Subsequent exposure of **10** to BBr_3 (6 equiv.) followed by hydrolysis afforded (±) nimbidiol (**3**) in 98% yield.



a. $LiN(SiMe_3)_2$, 1.5 equiv., -78 °C; b. Li Naphthalenide, 6.8 equiv., 0 °C; c. O_2, -78 °C; d. $SnCl_2$-HCl (aq.), 0 °C; e. BBr_3, CH_2Cl_2, 25 °C.

The foregoing synthesis of (±) nimbidiol is prominently characterized by its brevity which serves to underscore the synthetic power of sulfenium ion promoted polyene cascade annulations.

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3. In this regard, we have found that the higher electrophilicity and kinetic reactivity of episulfonium ions relative to mercuronium ions facilitates polyene cyclizations which are otherwise difficult to attain.[7]
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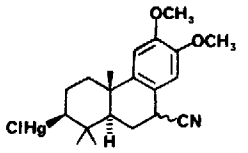
6. **9-Cyano-6,7-dimethoxy-1,2,3,4,4a,9,10,10a-octahydro-2-phenylthio-1,1,4a-trimethylphenanthrenes (9a,b).** An oven-dried 100 mL round-bottomed flask equipped with a magnetic stirring bar, rubber septum, and N_2 inlet was flushed with N_2, and then charged with $PhSOCH_3$ (0.261 g, 1.87 mmol) and CH_3NO_2 (20 mL). The solution was stirred at -30 °C and BF_3 (1.223 M in CH_3NO_2) (3.07 mL, 3.75 mmol) was added dropwise via syringe. The resulting solution was stirred for 2 min, whereupon the nitrile **8** (0.538 g, 1.28 mmol) in 2 mL of CH_3NO_2 was added dropwise via syringe over 5 min. The reaction mixture was then stirred at -30 °C for an additional h. The reaction was quenched with saturated aq. $NaHCO_3$ (50 mL), transferred to a separatory funnel, and extracted with ether (3 x 50 mL). The organic layer was washed with H_2O (50 mL), and brine (50 mL), then dried over $MgSO_4$. The solvents were removed in vacuo to provide the crude products. The resultant mixture was purified by chromatography on silica gel (1:4 ethyl acetate-hexane) to afford 0.635 g (85%) of a mixture of **9a** and **9b** as an amorphous white solid which was used directly for the preparation of **10**. Further purification of this mixture by high performance liquid chromatography permitted the separation of the individual nitriles. **9a:** mp 163-165 °C; ^1H NMR ($CDCl_3$) δ 1.03 (3H, s, CH_3), 1.28 (3H, s, CH_3), 1.33 (3H, s, CH_3), 1.34 (1H, m, CH_2), 1.38 (1H, dd, J = 1.4, 12.3 Hz, CH), 1.92-2.07 (2H, m, CH_2), 2.11 (1H, ddd, J = 12.3, 12.9, 14.3 Hz, CH_2), 2.26 (1H, apparent dt, J = 3.2, 13.0 Hz, CH_2), 3.29 (1H, ddd, J = 1.3, 6.7, 15.1 Hz, CH_2), 2.85 (1H, m, ΣJ = 16.7 Hz, CHSPh), 3.83 (3H, s, OCH_3), 3.87 (3H, s, OCH_3), 4.02 (1H, dd, J = 6.7, 11.9 Hz, CHCN), 6.69 (1H, s, ArH), 6.82 (1H, s, ArH), 7.18-7.42 (5H, m, SArH) ppm; ^{13}C NMR ($CDCl_3$) δ 17.70, 24.84, 24.85, 27.65, 29.89, 32.55, 37.49, 38.48, 38.95, 51.55, 55.93, 55.96, 60.47,

107.77, 110.33, 119.41, 122.08, 126.60, 128.91, 131.55, 136.28, 141.07, 147.54, 148.82 ppm; IR (KBr) cm^{-1} 3080-2840 (CH envelope), 2240 (CN), 1600, 1510. Anal. Calcd. for $C_{26}H_{31}NO_2S$: C, 74.07; H, 7.41. Found: C, 73.91; H, 7.61. **9b:** mp 172-174 °C; ^1H NMR ($CDCl_3$), δ 1.02 (3H, s, CH_3), 1.22 (3H, s, CH_3), 1.40 (3H, s, CH_3) 1.43-1.56 (1H, m, CH_2), 1.75 (1H, dd, J = 1.25, 12.0 Hz, CH), 1.93-2.08 (3H, m, CH2), 2.22-2.26 (2H, m, CH_2), 2.96 (1H, dd, J = 5.7 11.0 Hz, CHSPh), 3.83 (3H, s, OCH_3), 3.86 (3H, s, OCH_3), 4.05 (1H, m, ΣJ = 9.6 Hz, CHCN), 6.65 (1H, s, ArH), 6.69 (1H, s, ArH), 7.21-7.44 (5H, m, SArH) ppm; ^{13}C NMR ($CDCl_3$) δ 18.00, 23.96, 24.49, 27.80, 29.59, 32.19, 37.62, 38.16, 38.88, 49.71, 55.94, 55.94, 60.40, 108.03, 111.13, 119.26, 122.23, 126.61, 128.96, 131.55, 136.32, 141.50, 147.63, 149.12 ppm; IR (KBr) cm^{-1} 3080-2850 (CH envelope), 2240 (CN), 1600, 1500. Anal. Calcd. for $C_{26}H_{31}NO_2S$: C, 74.07; H, 7.41. Found: C, 73.91; H, 7.35.

7. In light of the success realized for the conversion of **8** → **9a,b** using $PhSOCH_3$-BF_3, it is of considerable interest that efforts to effect an analogous cyclization of **8** via the agency of $Hg(OTf)_2 \cdot PhNMe_2$[2a] gave rise to a diminutive yield (c.a., 31%) of the epimeric mercuriophenanthrenoids **11a,b.**



11a,b

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