was quickly[10] added 4.20 mL (1.26 mmol, 1.4 equiv) of the acetylide solution 7. The reaction mixture was warmed to −40 °C for 30 min, recooled to −78 °C, and quenched with 1.3 mL of saturated aqueous $KHCO_3$. After slowly warming to room temperature, a pale yellow organic layer separated from the white aqueous paste. Anhydrous sodium sulfate (200 mg) was added, and the mixture was concentrated in vacuo to 40% of its initial volume and was *placed under nitrogen*.[11] This mixture was diluted with 2% (v/v) triethylamine–ether (10 mL),[12] vigorously stirred, and the organic layer removed. The residual paste was similarly washed with fresh 2% triethylamine–ether (6 × 6 mL), the combined organic layers were dried (Na_2SO_4, 20 min), evaporated, and azeotropically dried with benzene (2 × 2 mL), affording a pale yellow oil (210 mg, 92%), which by TLC and NMR analyses was enyne **5** contaminated with only traces of **3**:[13] NMR ($CDCl_3$, neutralized[14]) δ 6.28 (d, 1 H, J = 6.2), 4.48 (m, 2 H), 3.76 (s, 3 H), 3.67 (s, 3 H), 3.03 (m, 2 H), 2.39 (t, 2 H, J = 7), 1.68 (m, 5 H); IR (CH_2Cl_2) 1735 (vs), 1634 (s); MS, 254 m/e (M^+).

Methyl 7-Hydroxy-11-methoxy-*trans*-5(*S*),6(*S*)-epoxyundeca-8(*Z*),10(*Z*)-dienoate (6). Crude **5** (160 mg, 0.63 mmol) was added to a 100-mL round-bottom flask and azeotropically dried with benzene (2 × 2 mL). To the flask were added a stirring bar and septum, and an inert atmosphere was established. Toluene (20 mL), pyridine (2 mL), and catalyst (Lindlar,[15] 32 mg) were added, and a hydrogen atmosphere was established. The reaction was monitored by TLC[16] at 15-min intervals and observed to be sluggish; more catalyst was introduced (19 mg), whereupon the reaction proceeded rapidly.[17] Upon completion the hydrogen atmosphere was removed and the reaction mixture was diluted with 20 mL of 2% triethylamine–ether. After filtration through cotton and evaporation in vacuo, the diene **6** was obtained in 97% yield (156 mg):[13] NMR ($CDCl_3$, neutralized[14]) δ 6.39–6.69 (m, 1 H), 5.97–6.06 (m, 1 H), 5.14–5.36 (m, 2 H), 4.33 (dd, 1 H, J = 8.7, 5.0), 3.68 (s, 3 H), 3.67 (s, 3 H), 2.79–2.92 (m, 2 H), 1.65 (m, 5 H); IR (CH_2Cl_2) 1735 (vs), 1650 (s) cm^{-1}; MS, m/e 238 ($m^+ - H_2O$).

Methyl *trans*-5(*S*),6(*S*)-Epoxy-11-oxoundeca-7(*E*),9(*E*)-dienoate (2). A solution of 156 mg (0.61 mmol) of **6** in dry methylene chloride (25 mL) was cooled to −40 °C and treated with triethylamine (0.26 mL, 1.83 mmol, 3 equiv) and mesyl chloride (94 μL, 1.22 mmol, 2 equiv). After 30 min, saturated aqueous $KHCO_3$ (1.0 mL) was introduced and the mixture was slowly warmed to room temperature. Anhydrous sodium sulfate (400 mg) was added and vigorously stirred. The organic layer was removed, and the aqueous paste remaining was washed with methylene chloride (4 × 6 mL). The combined organic layers were dried (Na_2SO_4, 15 min), filtered, and evaporated, leaving a yellow-orange paste. Extraction of this paste with 2% triethylamine–ether, evaporation, and azeotropic drying (benzene, 2 × 3 mL) yielded a yellow oil (132 mg, 97%), which by NMR and TLC was >95% pure dienal **2**:[18,19] NMR ($CDCl_3$, neutralized[14]) δ 9.57 (d, 1 H, J = 7.7), 5.81–7.35 (m, 4 H), 3.67 (s, 3 H), 2.87–3.26 (m, 2 H), 2.39 (t, 2 H, J = 7), 1.68 (m, 5 H); IR (CH_2Cl_2) 1735 (s), 1682 (s), 1642 (s), 990 (m) cm^{-1}.[20]

Registry No. **2**, 73958-00-6; **3**, 73427-12-0; **4**, 2798-73-4; **5**, 85749-89-9; **6**, 85749-90-2; **6** mesylate, 85749-91-3; **7**, 76584-33-3.

(11) At this stage excess **4** (prone to oxidation to *non*volatile products) was present in the reaction mixture. Thus the crude mixture containing **5** was kept under a nitrogen atmosphere until the remaining **4** could be removed.

(12) The product was subject to acid decomposition and therefore all the solvents used in its handling were adjusted to 2% triethylamine.

(13) The product was unstable to normal storage but could be kept in a −20 °C matrix of 2% triethylamine–benzene.

(14) The $CDCl_3$ was passed through a short column of basic alumina immediately prior to use to remove any acid present.

(15) Five percent palladium on calcium carbonate, Lindlar poisoned, was obtained from Engelhard Ind. and heated to 80 °C at 0.01 mmHg for 3 h prior to use.

(16) An ~15 μL aliquot of the reaction mixture was added to 100 μL of benzene over 500 μL of saturated aqueous cupric sulfate. After agitation the organic layer was spotted (silica gel plate) vs. **5** and eluted (three elutions) with 35% EtOAc–benzene: R_f(**5**) 0.505 (UV), R_f(**6**) 0.500(UV).

(17) Different samples of **5** required varying amounts of catalyst, which indicated the presence of variable amounts of catalyst poison. The best hydrogenation procedure was to add initially a 20% (wt/wt of substrate) portion of the catalyst, to monitor the progress of the reaction by TLC, and to add more catalyst until a reasonable reaction rate (3–5 h for completion) was realized.

(18) The product is chromatographically and spectroscopically identical with that prepared as per ref 3.

(19) The product may be further purified by preparative TLC on triethylamine-treated silica gel plates.

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1,3,4,9-Tetramethoxyphenalenyl System

R. C. Haddon,* A. M. Hirani, N. J. Kroloff, and J. H. Marshall

Bell Laboratories, Murray Hill, New Jersey 07974

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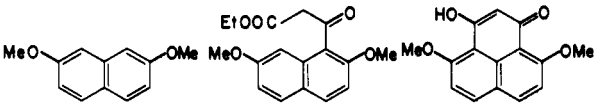
There has been considerable interest in the preparation of 1,3- and 1,9-disubstituted phenalene derivatives,[1,2] but little has been done to further elaborate the system. In the present study we report the synthesis and characterization of the 1,3,4,9-tetramethoxyphenalenyl system (together with associated compounds), in which the disubstitution pattern has been symmetrically extended.

Results and Discussion

As an entry to these derivatives we sought to prepare 4,9-dimethoxy-3-hydroxyphenalenone (**3**). This compound



was previously synthesized by Morrison and co-workers[3,4] via two different routes, both of which utilized 2,7-dimethoxynaphthalene (**1**) as starting material. These workers[3] obtained **3** from the polyphosphoric acid catalyzed condensation of **1** with malonic acid in a yield of 20%. They also found that **2** could be cyclized with polyphosphoric acid to give **3** in 75% yield.[4] The intermediate **2** was obtained by the reaction of **1** with ethylmalonyl chloride in nitrobenzene in the presence of aluminum chloride.[4] The yield of **2** was 64%, but the reaction was complicated by the formation of 1-acetyl-2,7-dimethoxynaphthalene as a byproduct.

We have found that **2** can be obtained from ethylmalonyl chloride and **1** (without the formation of byproducts) if 1,2-dichloroethane is used as the solvent and the temperature is maintained at or below room temperature. In addition we found concentrated sulfuric acid and especially anhydrous hydrogen fluoride to be more convenient than polyphosphoric acid for the cyclization of **2** to **3**.

The most curious result was obtained when we attempted to sublime **3**, for the sublimate consisted entirely

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(2) (a) Neidlein, R.; Behzadi, Z., *Chem.-Ztg.* **1978**, *102*, 24. (b) Franz, K. D.; Martin, R. L. *Tetrahedron* **1978**, *34*, 2147. (c) Haddon, R. C.; Wudl, F.; Kaplan, M. L.; Marshall, J. H.; Cais, R. E.; Bramwell, F. B. *J. Am. Chem. Soc.* **1978**, *100*, 7629.

(3) Frost, D. A.; Morrison, G. A. *J. Chem. Soc., Perkin, Trans. 1* **1973**, 2159.

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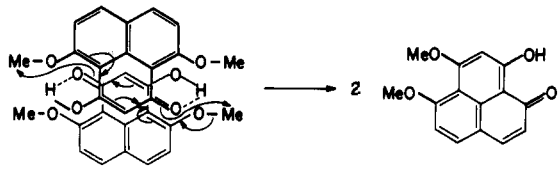
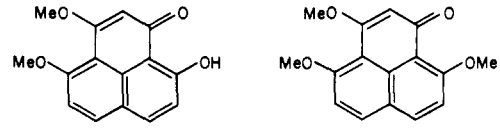
of 5. Apparently the strong intermolecular hydrogen bond



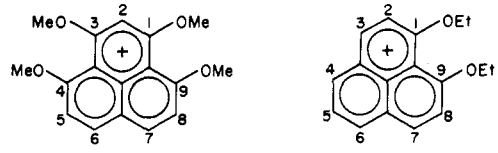
4 5

in 3[5] depressed the vapor pressure of the compound so that sublimation only occurs after rearrangement to the intramolecularly hydrogen-bonded 5. The dimeric structure 4 provides a reasonable candidate for the transition state of this unusual rearrangement. The rearrangement and decomposition of 3 on heating offers an explanation for the variability in melting point that has been observed for this compound.[3,4]

3,4,9-Trimethyoxyphenalenone (6) was obtained by treatment of an acetone solution of 3 with methyl *p*-toluenesulfonate in the presence of potassium carbonate. The final methylation was accomplished by reaction of trimethyloxonium tetrafluoroborate with 6 to produce the 1,3,4,9-tetramethoxyphenalenylium (7^+) salt.



5 6



7^+ 8^+

Compound $7^+,BF_4^-$ proved to be a stable yellow crystalline solid. It was reversibly reduced to the tetramethoxypenalenyl radical in acetonitrile, but at a potential 0.37 V more negative than the corresponding reduction potential for 8^+.[2b] The electron spin resonance specra of the two radicals were analyzed, and the proton hyperfine coupling constants (Table I) indicate a similar electron distribution in the two species.

Experimental Section

Ethyl 2,7-Dimethoxy-1-naphthoylacetate (2). A solution of 2,7-dimethoxynaphthalene (1) (37.6 g, 0.20 mol) and ethyl malonyl chloride (31.8 mL, 0.25 mol) was stirred in 1,2-dichloroethane under nitrogen. The solution was cooled in an ice bath, and when aluminum chloride (33.3 g, 0.25 mol) was slowly added the reaction mixture turned dark red. After being stirred overnight the reaction mixture was quenched with iced hydrochloric acid. The aqueous layer was extracted with dichloromethane, and the combined extracts were washed and dried over magnesium sulfate. The solvent was then removed on a rotary evaporator to give a viscous yellow-brown oil (56 g). The oil was purified by high-pressure liquid chromatography on a silica gel column (using ethyl acetate–hexane (20:80) as eluant) and afforded ethyl 2,7-dimethoxy-1-naphthoylacetate (43.9 g, 75%) as a pale yellow oil:[4] ^1H NMR (CD_3COCD_3, Me_4Si) δ 1.10 (t, J = 7 Hz, 3 H), 3.78 (s, 3 H), 3.81 (s, 3 H), 3.95 (s, 2 H), 4.10 (q, J = 7 Hz, 2 H), 6.92–7.95 (m, 5 H).

3-Hydroxy-4,9-dimethoxyphenalenone (3) [Sulfuric Acid Method]. Ethyl 2,7-dimethoxy-1-naphthoylacetate (2) (25.0 g, 0.086 mol) was slowly added to 200 mL of mechanically stirred sulfuric acid that was cooled with an ice bath. After being stirred for 3 h, the reaction mixture was hydrolyzed with ice water and initially neutralized with sodium hydroxide (260 g, 6.5 mol) and then taken to pH 7 with sodium bicarbonate. The solution was filtered, and the filtrate was repeatedly extracted with chloroform. All the extracts were combined, dried over anhydrous sodium sulfate, and evaporated down on a rotary evaporator to give a yellow solid (15.6 g, 71% yield). Crystallization from benzene–petroleum ether (charcoal) gave yellow prisms: mp 163.4–164.4 °C (lit. mp 153–154 °C,[4] 155–156 °C[3]); IR (cm^{-1}, CsI) 3340 (m, sh), 3010 (s), 2940 (s), 2840 (s), 2730 (m), 2630 (m, sh), 1650 (vs), 1580 (vs), 1510 (s), 1455 (s), 1438 (m), 1410 (m), 1370 (m), 1360 (s), 1325 (s), 1280 (vs), 1255 (vs), 1232 (vs), 1175 (vs), 1120 (m), 1030 (vs), 960 (s), 945 (w, sh), 835 (m), 800 (m), 750 (m), 735 (w), 655 (w), 490 (w), 425 (w); UV [λ_{max} nm (ϵ) (methylene chloride)] 435 (2300, sh), 409 (5300, sh), 398 (6300, sh), 363 (17 900), 248 (21 600), 237 (17 200), 227 (15 000, sh); ^1H NMR ($CDCl_3$, Me_4Si) δ 4.18 (s, 6 H), 6.25 (s, 1 H), AB pattern δ_A 7.30, δ_B 8.02 (J_{AB} = 9 Hz, 4 H). Anal. Calcd for $C_{15}H_{12}O_4$: C, 70.31; H, 4.72; O, 24.97. Found: C, 70.09; H, 4.81; O, 24.88.

Table I. Hyperfine Proton Coupling Constants of Phenalenyl Radicals

7[a,c]		8[b,c]	
positions	coupling constants, G	positions	coupling constants, G
OCH_3	0.52	OCH_2	0.65
$H_{6,7}$	6.14	$H_{3,7}/H_{4,6}$	6.00, 6.16
H_2	1.55	$H_{2,8}$	1.53
$H_{5,8}$	1.55	H_5	1.76

[a] Solution in CH_3CN; g = 2.0029. [b] Solution in CH_2Cl_2/CH_3CN; g = 2.0026. [c] Experimental details are given in ref 2c.

3-Hydroxy-4,9-dimethoxyphenalenone (3) [Hydrogen Fluoride Method]. Crude ethyl 2,7-dimethoxy-1-naphthoylacetate (2) (7.17 g, 0.024 mol) was added to 75 mL of anhydrous hydrogen fluoride with stirring in a (conventional) polyethylene bottle. The dark red solution was allowed to stir overnight, and then the HF was removed under a stream of nitrogen. When all of the HF had evaporated and only a dark solid remained, 120 mL of water and 120 mL of chloroform were added. The aqueous layer was extracted with chloroform after all of the solid had been dissolved (1 h). The aqueous layer, which was initially at a pH of 3, was slowly neutralized with sodium bicarbonate. When 3.5 g (0.042 mol) of base had been added, a yellow precipitate appeared. The precipitation continued until, after 15 min, the reaction solution had become a fluffy yellow semisolid. Filtration of the wet precipitate left a bright yellow solid, which was then dried in a vacuum oven, leaving 5.13 g of product (83% yield), identical in all respects to the one obtained by the sulfuric acid method.

Attempted Sublimation of 3-Hydroxy-4,9-dimethoxyphenalenone (3)—Preparation of 3,4-Dimethoxy-9-hydroxyphenalenone (5). Sublimation of 3-hydroxy-4,9-dimethoxyphenalenone (3) (5.6 g, 21.8 mmol) at 160 °C (0.005 mm) gave 3.0 g of a yellow solid (together with an involatile black residue). The sublimate was recrystallized from ethanol, resublimed, and then recrystallized from dichloroethane/hexane to give shiny yellow needles of 3,4-dimethoxy-9-hydroxyphenalenone (5): mp 201.0–201.4 °C (lit.[6] mp 201 °C); IR (cm^{-1}, CsI) 3450 (w), 1625 (s), 1570 (m) 1495 (w), 1456 (w), 1405 (w), 1365 (w), 1343 (w) 1290 (w), 1245 (m), 1225 (s), 1178 (m), 1137 (w), 1110 (m), 1000 (s), 920 (w), 850 (m), 835 (m), 825 (m), 800 (w), 660 (w), 546 (w), 510 (w), 453 (w), 400 (w); UV [λ_{max} nm (ϵ) (hexane)] 235 (21 600), 252 (sh, 15 200), 271 (7100), 282 (5800), 309 (sh, 3500), 363 (15 300), 315 (sh, 13 400), 385 (sh, 11 000), 393 (11 000), 417 (7300), 424 (8600); ^1H NMR ($CDCl_3$, Me_4Si) δ 4.03 (s, 3 H), 4.08 (s, 3 H), 6.40 (s, 1 H), two AB patterns δ_A 7.02, δ_A 7.08, δ_B 7.88, δ_B 7.92 (J_{AB} = 9 Hz, 4 H). Anal. Calcd for $C_{15}H_{12}O_4$: C, 70.29; H, 4.72. Found: C, 70.01; H, 4.56.

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3,4,9-Trimethoxyphenalenone (6). The reaction was carried out under an argon atmosphere, and all of the glassware was flame dried. 3-Hydroxy-4,9-dimethoxyphenalenone (3) (1.0 g, 0.0039 mol) was dissolved in acetone (dried over alumina). Anhydrous potassium carbonate (2.0 g, 0.01 mol) was added to the flask while the solution was mechanically stirred. After 10 min, methyl *p*-toluenesulfonate (1.5 mL, 0.01 mol) was slowly added to the flask and the reaction mixture was taken to reflux. After 16 h the solution was filtered and the filtrate was evaporated down on a rotary evaporator to give a viscous pale yellow oil. The compound was purified by high-pressure liquid chromatography on a silica gel column (using methanol–methylenechloride (5:95) as eluant) to give 3,4,9-trimethoxyphenalenone (0.43 g, 41% yield) as a yellow solid: mp 166.0–166.2 °C); IR 9 Hz, CsI) 2940 (w), 2840 (w), 1650 (vs), 1578 (s), 1540 (m), 1508 (m), 1455 (m), 1392 (m), 1366 (w), 1306 (m), 1266 (s), 1220 (s), 1170 (s), 1090 (w), 1038 (s), 1000 (w), 958 (w), 835 (m), 804 (w), 785 (w), 662 (w), 510 (w), 430 (w); UV [λ_{max} nm (ϵ) (hexane)] 413 (3300, sh), 392 (6000, sh), 362 (14400), 323 (5500, sh), 250 (22200); ^{1}H NMR ($CDCl_3$, Me_4Si) δ 3.96 (s, 3 H), 4.08 (s, 3 H), 4.15 (s, 3 H), 6.26 (s, 1 H), two AB patterns δ_A 7.20, δ_A 7.28, δ_B 7.91, δ_B 7.98 (J_{AB} = 9 Hz, 4 H). Anal. Calcd for $C_{16}H_{14}O_4$: C, 71.10; H, 5.22. Found: C, 70.88; H, 5.50.

1,3,4,9-Tetramethoxyphenalenylium Tetrafluoroborate ($7^+,BF_4^-$). Trimethoxyphenalenone (6) (0.135 g, 0.5 mmol) was dissolved in 5 mL of dry 1,2-dichloroethane under nitrogen, and trimethyloxonium tetrafluoroborate (0.1 g, 0.7 mmol) was added with stirring. After 3 h the mixture was filtered and the precipitate isolated (0.135 g, 72%). Recrsytallization from acetonitrile gave yellow needles: mp >300 °C; IR (cm^{-1}, CsI) 3450 (w,br), 1615 (s), 1600 (s, sh), 1561 (s), 1500 (m), 1488 (m, sh), 1465 (w), 1393 (w), 1354 (w), 1285 (vs), 1247 (m), 1230 (m), 1182 (m), 1055 (s), 1020 (vs), 950 (w), 901 (w), 835 (m), 655 (vw), 515 (vw); UV [λ_{max} nm (ϵ) (acetonitrile)] 423 (24100), 399 (19900) 374 (19300), 267 (11000, sh), 236 (22000), 220 (23900); ^{1}H NMR (CD_3CN, Me_4Si) δ 4.32 (s, 6 H), 4.38 (s, 6 H), 7.05 (s, 1 H), AB pattern δ_A 7.67, δ_B 8.67 (J_{AB} = 9 Hz, 4 H). Anal. Calcd for $C_{17}H_{17}O_4BF_4$: C, 54.87; H, 4.60; B, 2.91; F, 20.41. Found: C, 54.77; H, 4.64, B, 3.01; F, 20.11.

Acknowledgment. We are grateful to M. L. Kaplan and R. G. Cooke for useful discussions.

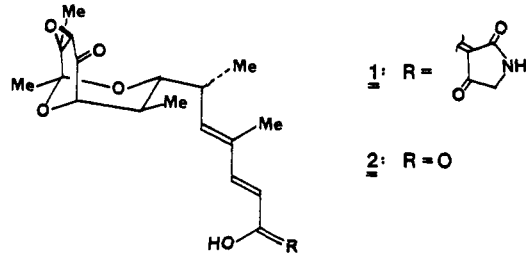
Registry No. 1, 3469-26-9; 2, 71094-90-1; 3, 52588-83-7; 5, 85736-07-8; 6, 85736-08-9; 7^+, 85736-09-0; $7^+BF_4^-$, 85736-10-3; ethyl malonyl chloride, 36239-09-5.

Communications

Total Synthesis of Tirandamycin. A Short, Efficient Synthesis of the Ireland Alcohol

Summary: Alcohol 3, comprising the bicyclic portion of the antibiotic tirandamycin, has been synthesized in seven steps from 2,3-dimethylfuran and aldehyde 5. The key transformation in this scheme is conversion of furan alcohol 4 into pyranone 11.

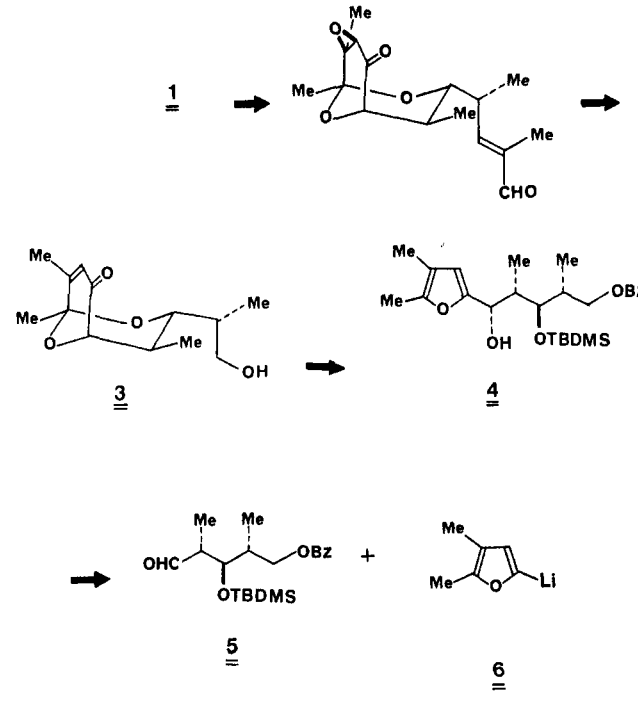
Sir: Tirandamycin (1)[1,2] is a member of the 3-dienoyltetramic acid family of antibiotics. Several groups have



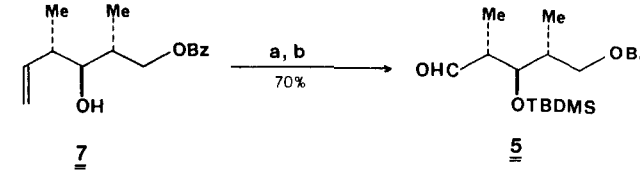
been involved in the development of methodology for the total synthesis of this molecule.[3-6] These efforts have recently culminated in the synthesis of (+)-tirandamycic acid (2), a degradation product of tirandamycin, by Ireland and his co-workers, beginning with D-glucose.[4] In this communication, we report a short, efficient synthesis of alcohol 3 (the Ireland alcohol) in racemic form.

Alcohol 3 was prepared previously in the Ireland synthesis of tirandamycin acid and was chosen as a key intermediate in our strategy for the synthesis of tiran-

Scheme I



Scheme II[a]



[a] *t*-$BuMe_2SiCl$, imidazole, DMF, room temperature; (b) O_3, CH_2Cl_2, −20 °C; HOAc, Zn, room temperature.

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