Synthesis of Ring-Alkylated Isoproterenol Derivatives

Allen Reitz, Mitchell A. Avery, Michael S. Verlander, and Murray Goodman*

Department of Chemistry, B-014, University of California, San Diego, La Jolla, California 92093

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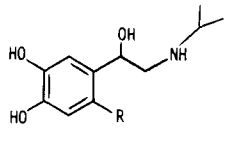
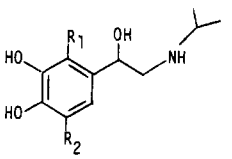
2-Propyl-, 5-propyl-, and 6-propylisoproterenols (**2a**, **2b**, and **1d**, respectively) have been synthesized as models for polymer drug conjugates. Key intermediates were the propenylbenzaldehydes **3a–c**. The (isopropylamino)phenethanol side chain was constructed from the aldehyde functionality by the method of Avery et al.[2] The benzaldehyde **3b** was prepared from 3,4-dihydroxybenzaldehyde (**7**) by selective alkylation at the 4-hydroxyl followed by Claisen rearrangement and benzylation of the phenolic hydroxyls. Selective alkylation at the 3-hydroxyl of **7** could be effected with 2 equiv of base. The benzaldehyde **3c** was prepared by the utilization of the aryllithium intermediate **16a**. Methods to form the 2-, 5-, and 6-(3-hydroxypropyl)isoproterenols, useful for attachment to polymer carriers, and the biological activity of **2a**, **2b**, and **1d** are briefly discussed.

One facet of our goal[1] of developing active, carrier-bound, β-adrenergic drugs has been to prepare functionalized derivatives of the catecholamine isoproterenol (**1a**).



1a R=H
1b R=NH_2
1c R=NH–C(=O)–CH$_3$
1d R=nC_3H_7

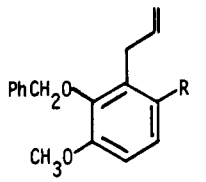


2a R_1=nC_3H_7, R_2=H
2b R_1=H, R_2=nC_3H_7

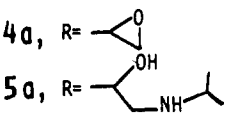
Our strategy consists of utilizing the derivatized portion of the catecholamine as a point of attachment to a carrier molecule. These goals have been met in part, as was previously reported,[2] by the synthesis of 6-aminoisoproterenol (**1b**) and its *N*-acetyl derivative **1c**. As a continuation of these studies, we have prepared three alkyl derivatives of **1a**, 2-, 5-, and 6-propylisoproterenol (**2a**, **2b**, and **1d**, respectively)[3]. These three ring-alkylated isoproterenols were prepared for biological testing as models for the analogous 2-, 5-, and 6-(3-hydroxypropyl)-isoproterenols which could be derivatized readily (at the primary hydroxyl) by a suitably activated carrier molecule.

Our synthetic approach was to first prepare the propenylbenzaldehydes **3a–c**. We could then make use of previously reported methodology[2,4] to convert the aryl aldehydes into vicinal hydroxy amines. This consisted of epoxide formation via dimethylsulfonium methylide[5] (e.g., epoxide **4a**) followed by ring opening with isopropyl amine (e.g., protected catecholamine **5a**). Deprotection would then afford the desired catecholamines **2a**, **2b**, and **1d**.

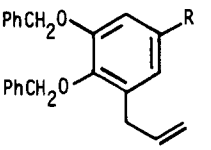
The aldehyde **3a** is a known compound[6] prepared from *O*-allylisovanillan by Claisen rearrangement,[7] followed by



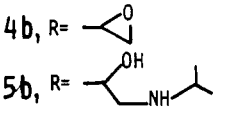
3a, R=CHO



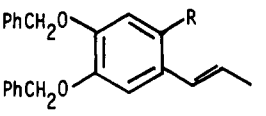
4a, R=
5a, R=



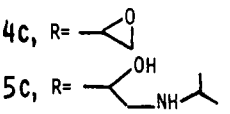
3b, R=CHO



4b, R=
5b, R=

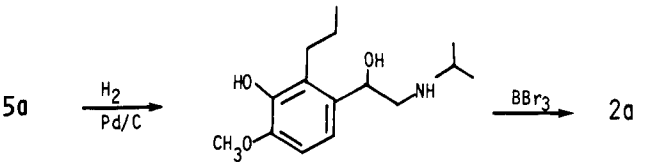


3c, R=CHO



4c, R=
5c, R=

benzylation of the phenolic hydroxyl. Compound **3a** was converted to **5a** as indicated above. The deprotection of **5a** to give **2a** was effected by hydrogenation to yield the phenol **6**, followed by removal of the methyl ether with BBr_3.[8]



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The aldehyde **3b** was synthesized from 3,4-dihydroxybenzaldehyde **7** in the following manner. Treatment of **7** with allyl bromide and 1 equiv of NaOEt produced the *O*-allyl ether **8** which was heated at 220 °C in a sealed tube, giving the catechol **9** in 89% yield after crystallization. Standard protection[9] then afforded the aldehyde **3b**.

(1) (a) M. S. Verlander, J. C. Venter, M. Goodman, N. O. Kaplan, and B. Saks, *Proc. Natl. Acad. Sci. U.S.A.*, **70**, 1214 (1976); (b) J. C. Venter, M. S. Verlander, N. O. Kaplan, M. Goodman, J. Ross, Jr., and S. Sesayama in "Polymeric Delivery Systems", Midland Macromolecular Symposium No. 5, Gordon and Breach, London, 1978; (c) K. L. Melmon, M. S. Verlander, L. Krasny, M. Goodman, N. Kaplan, N. Castagnoli, and P. Insel in "Proceedings of the 4th International Symposium on Catecholamines", Pergamon Press, Oxford, 1978, p 474.

(2) M. Avery, M. Verlander, and M. Goodman, *J. Org. Chem.*, **45**, 2750 (1980).

(3) 2-Propylisoproterenol (**2a**) has been previously synthesized via a different route. A. Mentrup, K. Schromm, K. Zeile, and O. Thoma, U.S. Patent 3 657 244, 1972.

(4) S. Sohda, M. Fujimoto, T. Tamegai, and N. Hirose, *J. Med. Chem.*, **22**, 279 (1979).

(5) E. Corey and M. Chaykovsky, *J. Am. Chem.*, **87**, 1353 (1965).

(6) F. Caesar and A. Mondon, *Chem. Ber.*, **101**, 990 (1968).

(7) L. Claisen, *Chem. Ber.*, **45**, 3157 (1912).

(8) J. McOmie and D. West, *Org. Synth.*, **5**, 412 (1968).

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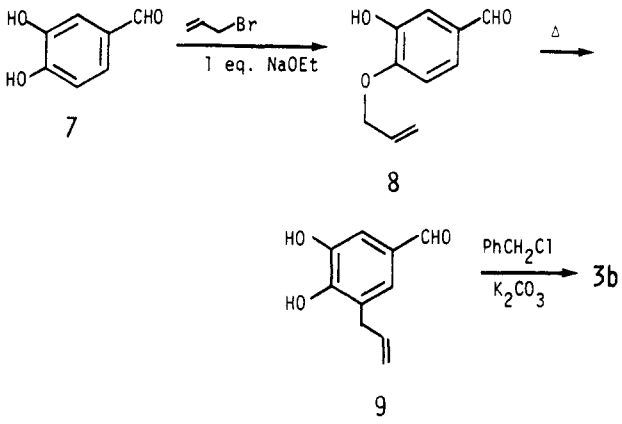
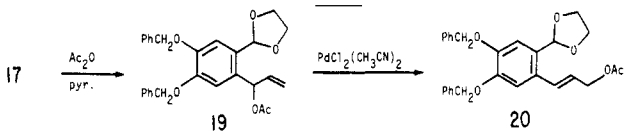


The observation that 3,4-dihydroxybenzaldehyde (7) could be O-alkylated predominantly at the 4-position to give 8 suggested, not unexpectedly, that the phenoxide anion **10a** was strongly stabilized by the para aldehyde functionality (**10a,b**, Scheme I). However, treatment of 7 with 2 equiv of NaH in refluxing THF followed by the addition of allyl iodide and chromatography led to the vanillan derivative **12** as the major O-alkylation product in 17% yield. Also produced in this reaction was the ether 8, and the ratio of **12** to 8 was 4:1. The predominant formation of the *O*-allyl ether **12** could be due to the existence of dianion **11** and its ability to separate the additional charge. Compound **11** could undergo dialkylation to produce the unstable ether **11c** which would afford **12** upon aqueous workup.

The aldehyde **3c** was prepared by a somewhat different route involving the aryllithium intermediate **16a** (Scheme II). The sequence for the preparation of **3c** began with readily available 6-bromopiperonal (**13**). Treatment of **13** with anhydrous $AlCl_3$ followed by refluxing with aqueous HCl in THF (trace of KI) gave the catechol **14**. Protection of **14** with benzyl chloride and K_2CO_3 proceeded normally to give the diether **15**, and this aldehyde was converted to the cyclic acetal **16** by azeotropic removal of water from a mixture of *p*-toluenesulfonic acid, ethylene glycol, benzene, and **15**. The acetal **16** was smoothly transmetalated by reaction in THF at low temperature with 2 equiv of *n*-butyllithium.[10] The resulting suspension of **16a** was treated with distilled acrolein to give a nearby quantitative yield of allylic alcohol **17**. This alcohol, when treated with 0 °C with $SOCl_2$ and pyridine in ether, gave a mixture of primary and secondary chlorides in addition to partial acetal cleavage. However, the same reaction conducted at −78 °C led cleanly to the primary halide **18**. Reductive cleavage of the halide of **18** with $LiAlH_4$ in THF followed by addition of aqueous HCl gave the aldehyde **3c** in 46% yield from the allylic alcohol **17**. This aldehyde was then used to eventually form 6-propylisoproterenol.

Since our ultimate goal was to obtain hydroxy-terminated propyl derivatives (obtainable from aldehydes **3a** and **3b** by hydroboration after protection of the aldehyde function) of the catecholamines **2a**, **2b**, and **1d**, we decided to explore one final route which could lead to a 3-hydroxypropyl analogue of **1d**. Treatment of the allylic alcohol **17** with Ac_2O and pyridine gave the allylic acetate **19**. Rearrangement of **19** with $PdCl_2(CH_3CN)_2$ led to the expected product **20** in excellent yield. Although we were



able to convert allylic acetate **20** into 6-(3-hydroxypropyl)isoproterenol on an exploratory scale, we did not pursue the synthesis past this point due to the low biological activity of 6-propylisoproterenol (**1d**).

Treatment of the aldehydes **3a–c** with dimethylsulfonium methylide proceeded without incident to give the corresponding epoxides **4a–c** in better than 90% yield. Epoxide opening with excess isopropylamine in refluxing ethanol then gave the protected catecholamines **5a** (37%), **5b** (69%), and **5c** (30%). These protected catecholamines were then exhaustively hydrogenated over 10% Pd/C in acetic acid, and the desired products **6**, **2b**, and **1d** were obtained in at least 70% yield.

The 2-, 5-, and 6-propylisoproterenols (**2a**, **2b**, and **1d**, respectively) have been tested in vitro for β-adrenergic activity (results to be reported elsewhere). The 5- and 6-propylisoproterenols (**2b** and **1d**, respectively) are inactive, and 2-propylisoproterenol (**2a**) is active but shows significantly lower activity than the parent compound isoproterenol (**1a**).

Experimental Section

All melting points were recorded on a Thomas-Hoover capillary melting point apparatus and are uncorrected. IR spectra were taken on a Perkin-Elmer 180 spectrophotometer. High-resolution proton NMR spectra were taken in the Fourier transform mode on a Varian HR-220 spectrometer equipped with a Nicolet 1080 computer. Chemical shifts are reported in parts per million downfield from Me_4Si. Mass spectra were determined on an LKB-9000 A mass spectrometer. All elemental analysis were performed by Galbraith Laboratories.

4-(Allyloxy)-3-hydroxybenzaldehyde (8). To a dry 500-mL flask equipped with magnetic stirring and an argon inlet was added dry ethanol (250 mL). Sodium metal (washed free of mineral oil; 2.2 g, 0.096 mol) was slowly added in small pieces. When the addition was complete, 3,4-dihydroxybenzaldehyde (7; 12 g, 0.0869 mol) was added at once. The mixture was stirred 30 min, and allyl iodide was added (15.1 g, 8.5 mL, 0.090 mol). After 2 days the solution was poured into water (1 L), and extracted with ether (3 × 200 mL); the combined ether layer was washed with saturated aqueous NaCl (2 × 100 mL), dried over $MgSO_4$, and filtered, and the solvent was removed. The resulting fragrant oil was chromatographed on silica gel (300 g) with EtOAc–hexanes (1:3), giving 8 (6 g or 38.8% yield) as a clear oil: bp 220 °C; NMR ($CDCl_3$) δ 4.71 (d, 2 H, J = 7.5 Hz), 5.42 (m, 2 H), 6.08 (m, 1 H), 6.97 (d, 1 H, J = 9 Hz), 7.44 (m, 2 H), 9.93 (s, 1 H). Anal. Calcd for C, 67.34; H, 5.66; O, 26.94. Found: C, 67.11; H, 5.70; O, 26.70.

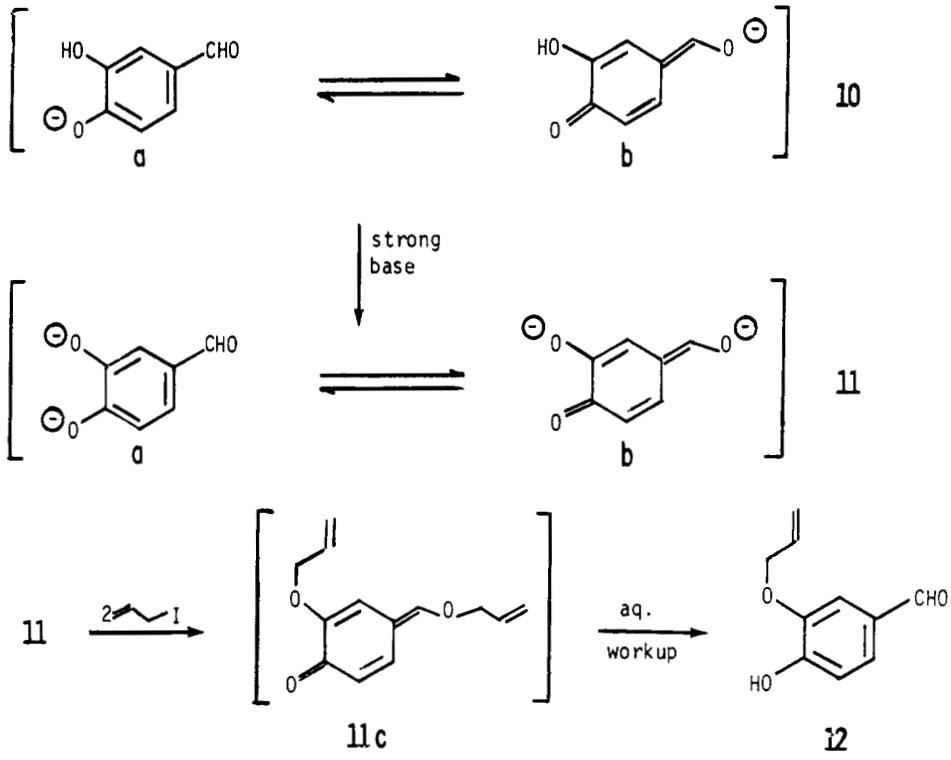
3,4-Dihydroxy-5-(prop-2-enyl)benzaldehyde (9). The *O*-allyl ether 8 (2 g or 11.2 mmol) was heated at 230 °C for 2 h in a sealed tube. Crystallization of the crude product gave 9: 1.78 g (89% yield); mp 150–153 °C; NMR ($(CD_3)_2CO$) δ 3.46 (d, 2 H, J = 7.5 Hz), 5.1 (m, 2 H), 6.02 (m, 1 H), 7.28 (s, 1 H), 7.30 (s, 1 H), 9.76 (s, 1 H). Anal. Calcd for C, 67.34; H, 5.66; O, 26.94. Found: C, 67.20; H, 5.81; O, 26.85.

3,4-Bis(benzyloxy)-5-(prop-2-enyl)benzaldehyde (3b). To a 100-mL flask equipped with magnetic stirring, a reflux condenser, and an argon inlet were added ethanol (50 mL), pulverized Na_2CO_3 (3.3 g, 30.9 mmol), benzyl chloride (2.4 g, 2.2 mL, 18.5 mmol), KI (50 mg), and the catechol 9 (1.1 g, 6.18 mmol). The mixture was refluxed for 8 h, cooled to room temperature, and added to aqueous 5% HCl (200 mL). Ether was added (20 mL) and the aqueous phase removed. The organic layer was washed with water (2 × 50 mL) and saturated aqueous $NaHCO_3$, (3 × 70 mL) dried over $MgSO_4$, and filtered, and the solvent was removed by rotary evaporation. The material was placed under high vacuum overnight and then chromatographed on silica gel (80 g). The product, **3b** (1.65 g or 76% yield), would not crystallize: NMR ($CDCl_3$) δ 3.41 (d, 2 H, J = 7.5 Hz), 5.08 (m, 2 H), 5.13 (s,

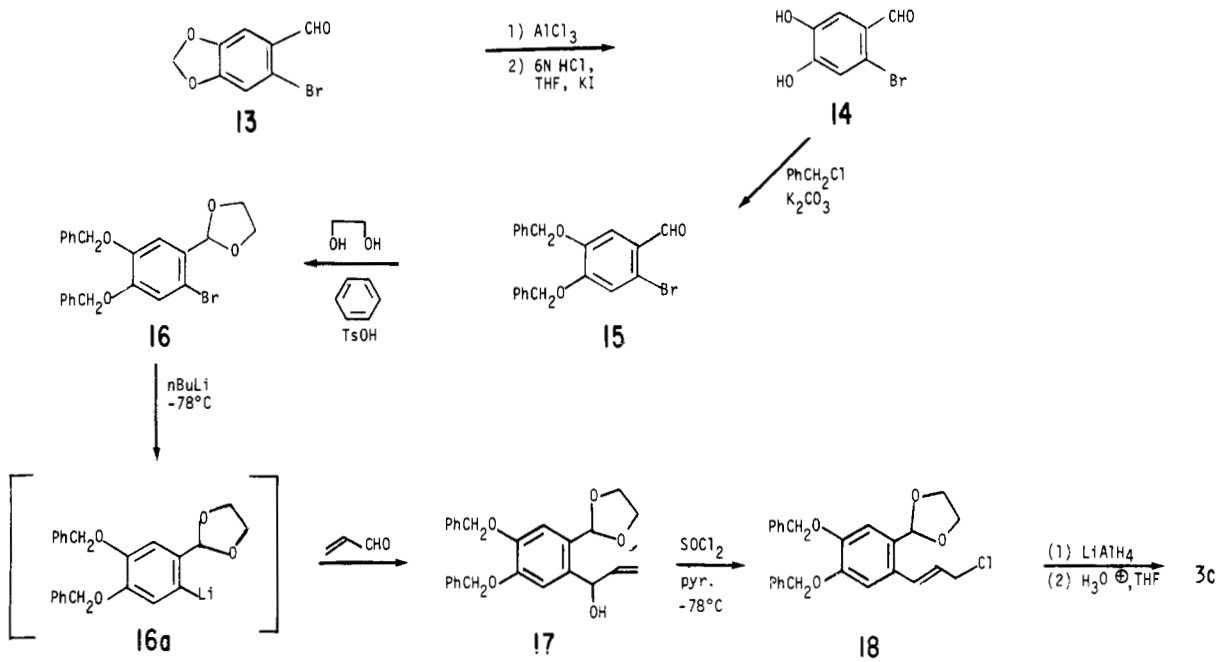
(9) K. Merz and J. Fink, *Arch. Pharm.*, **289**, 347 (1956); J. Suh, C. Judd, and F. Kaminski, *J. Med. Chem.*, **10**, 262 (1967).

(10) For an example of the use of an aryllithium intermediate in the presence of a 1,3-dioxolanyl group see S. Thames and J. McCleskey, *J. Heterocycl. Chem.*, **3**, 104 (1966).

Scheme I



Scheme II



2 H), 5.20 (s, 2 H), 5.89 (m, 1 H), 7.38 (m, 12 H), 9.84 (s, 1 H). Anal. Calcd: C, 80.42; H, 6.19; O, 13.39. Found: C, 80.46; H, 6.11; O, 13.13.

3-(Allyloxy)-4-hydroxybenzaldehyde (12). To a dry two-necked flask with a nitrogen inlet was added NaH (50% oil dispersion; 7.65 g, 2.2 equiv), and the oil was washed away with 8 mL of dry hexanes. 3,4-Dihydroxybenzaldehyde (7; 10 g, 72.4 mmol) in distilled THF (30 mL) was added by syringe, and the solution was stirred at room temperature for 30 min. Allyl iodide (13.8 mL, 2.1 equiv) was then added via syringe, and the mixture was refluxed for 4 h. The mixture was added to H_2O, extracted into EtOAc, and washed twice with brine solution. The organics were dried ($MgSO_4$) and filtered, and the solvent was evaporated. The crude product was chromatographed on a silica gel column (70–270 mesh, 350 g) in EtOAc/hexanes (25/75). The resulting yellow solid **12** had a pleasant odor: 2.24 g (17.4% yield); mp 58–61 °C; NMR ($CDCl_3$) δ 4.74 (d, 2 H), 5.44 (t, 2 H), 6.1 (m, 1 H), 6.23 (s, 1 H), 7.06 (d, 1 H), 7.48 (d, 2 H), 9.63 (s, 1 H); mass spectrum, *m/e* 218 (M + C_3H_4), 217, 203, 178 (M^+), 177, 149, 91. Anal. Calcd: C, 67.40; H, 5.67; O, 26.94. Found; C, 67.67; H, 5.82; O, 26.70.

3,4-Bis(benzyloxy)-6-bromobenzaldehyde (15). To a suspension of anhydrous $AlCl_3$ (30 g, 5 equiv) in 200 mL of dry CH_2Cl_2 under N_2 was added 6-bromopiperonal (**13**; 10 g, 0.0437 mol) dissolved in 100 mL of dry CH_2Cl_2. The mixture was stirred for 2 h, aqueous 6 N HCl (500 mL) was added, and the organic phase was separated and then washed water (3 × 100 mL). The resulting organic phase was dried over $MgSO_4$, filtered, and crystallized to give 3-(chloromethoxy)-4-hydroxy-6-bromobenzaldehyde in nearby quantitative yield: NMR $(CD_3)_2CO$ δ 6.1 (s, 2 H), 7.25 (s, 1 H), 7.7 (s, 1 H), 10.15 (s, 1 H). Addition of THF (200 mL), aqueous 6 N HCl (200 mL), and KI (1 g) to the crude chloro ether

followed by overnight reflux under N_2 resulted in cleavage of the chloro ether. The mixture was cooled to ambient temperature, and EtOAc (300 mL) was added. The organic layer was separated and washed with (3 × 100 mL) water and then saturated aqueous NaCl (1 × 100 mL). The organic phase was dried over Na_2SO_4, filtered, and the solvent removed to give 3,4-dihydroxy-6-bromobenzaldehyde (**14**). NMR ($(CD_3)_2SO$) δ 7.0 (s, 1 H), 7.2 (s, 1 H), 9.9 (s, 1 H). This product was quite pure and could be crystallized from ether but was used directly for the next step. The catechol **14** was dissolved in ethanol (250 mL), and pulverized K_2CO_3 was added (28 g, 0.2 mol) with stirring under N_2. Benzyl chloride was then added (0.16 mol, 2.0 g) followed by a trace of KI (200 mg). The mixture was refluxed for 18 h, cooled, and carefully treated with aqueous 6 N HCl (ca. 200 mL). After the mixture was stirred for 30 min at 25 °C, ether was added (500 mL), and the aqueous phase was removed. The organic layer was washed with saturated aqueous $NaHCO_3$ (3 × 100 mL), the organic phase was dried over $MgSO_4$ and filtered, and the solvent was removed. The resulting solid was recrystallized from ether to give **15**: 12 g (69.3% yield from **13**); mp 99–100.5 °C; NMR ($CDCl_3$) δ 5.1 (s, 4 H), 7.1 (s, 1 H), 7.3 (m, 10 H), 7.4 (s, 1 H), 10.05 (s, 1 H); IR (Nujol) 1680 (s), 1590 (s), 1450 (s), 1380 (s), 1150 cm^{-1}. Anal. Calcd: C, 63.49; H, 4.31; O, 12.08. Found: C, 63.22; H, 4.52; O, 12.44.

1-(1,3-Dioxolan-2-yl)-3,4-bis(benzyloxy)-6-bromobenzene (16). To the aldehyde **15** (2 g or 5.04 mmol) was added benzene (80 mL), ethylene glycol (10 mL), and *p*-toluenesulfonic acid (50 mg). The solution was heated at reflux under N_2, and water was removed by using a Dean–Stark apparatus. After 2 h, the mixture was cooled to room temperature, added to water (200 mL), and then extracted with Et_2O (3 × 75 mL). The combined organic phase was washed saturated aqueous $NaHCO_3$ (3 × 50 mL), dried over $MgSO_4$, and filtered through a pad of alumina, and the solvent was removed. The oily product crystallized from ether/hexanes to give **16**: 2.1 g (95% yield); mp 61–63 °C; NMR ($CDCl_3$) δ 4.04 (m, 4 H), 5.12 (s, 2 H), 5.14 (s, 2 H), 5.98 (s, 1 H), 7.08 (s, 1 H), 7.18 (s, 1 H), 7.36 (m, 10 H); mass spectrum, *m/e* 443, 441 (1:1, M^+), 399, 397, 351, 349, 308, 306.

3,4-Bis(benzyloxy)-1-(1,3-dioxolan-2-yl)-6-(1-hydroxyprop-2-enyl)benzene (17). To a dry, 250-mL, three-necked flask equipped with an Ar inlet, stopper, and septum and with magnetic stirring (neck joints are parafilmed) was added dry ether (150 mL) via syringe. The solution was cooled to −78 °C and *n*-butyllithium (1.6 M in hexanes, 5 mL, 0.008 mmol) was added via syringe. The bromo acetal **16** (1.75 g, 0.004 mol) dissolved in dry ether (30 mL) was added via syringe to the *n*-butyllithium solution over a 15-min period. A white suspension formed immediately. After 1 h at −78 °C, freshly distilled acrolein (0.44 g, 0.008 mol) was added at once via syringe. The resulting solution was allowed to warm to room temperature and was stirred an additional 2 h. The reaction mixture was added to water (100 mL), and the ether layer was separated and washed with water (2 × 50 mL) and then saturated aqueous NaCl (1 × 50 mL). The solvent was removed and the crude material was chromatographed quickly over alumina. This gave a clear oil of **17**: 1.57 g (95% yield); NMR ($CDCl_3$) δ 4.04 (m, 4 H), 5.14 (s, 4 H), 5.35 (m, 2 H), 5.5 (m, 1 H), 5.98 (s, 1 H), 6.0 (m, 1 H), 7.04 (s, 1 H), 7.16 (s, 1 H), 7.40 (m, 10 H); mass spectrum, *m/e* 418 (M^+), 356, 265, 237, 219, 209.

3,4-Bis(benzyloxy)-6-(3-chloroprop-1-enyl)-1-(1,3-dioxolan-2-yl)benzene (18). To a three-necked flask equipped with a septum, Ar inlet, and stopper and with magnetic stirring was added a solution of the allylic alcohol **17** (1.3 g, 3.11 mmol) in dry ether (30 mL) and dry pyridine (0.3 mL, 3.6 mmol) via syringe. The solution was then cooled to −78 °C. In a separate flask were added distilled $SOCl_2$ (0.26 mL, 3.6 mmol), dry ether (3 mL), and dry pyridine (0.1 mL) via syringe. The resulting solution was then added to the allylic alcohol over a 15-min period via syringe. After 30 min, the mixture was added to saturated aqueous $NaHCO_3$ (100 mL). Ether was added (100 mL), and the aqueous phase was removed. The organic phase was then washed with cold 1% aqueous HCl (2 × 30 mL) and saturated aqueous $NaHCO_3$ (2 × 30 mL), dried over $MgSO_4$, and filtered, and the solvent was removed. The resulting light yellow oil of **18** slowly solidified under high vacuum but also turned dark green after a short period of time. Accordingly, it was used directly for the next step: NMR ($(CD_3)_2SO$) δ 4.0 (m, 4 H), 4.4 (d, 2 H, J = 7 Hz), 5.14 (s, 2 H), 5.22 (s, 2 H), 5.88 (s, 1 H), 6.30 (dt, 1 H, $^3J_{AM}$ = 8.8 Hz; $^3J_{MX}$ = 16 Hz), 7.02 (d, 1 H, $^3J_{XM}$ = 16 Hz), 7.14 (s, 1 H), 7.28 (s, 1 H), 7.42 (m, 10 H); mass spectrum, *m/e* 438, 436 ($M^+ + 2$, M^+), 416, 394, 392, 373, 374, 375, 356, 357, 358, 343, 318.

3,4-Bis(benzyloxy)-6-(prop-1-enyl)benzaldehyde (3c). The allylic chloride **18** from the above procedure was dissolved in dry THF (10 mL) and added to a suspension of excess $LiAlH_4$ (200 mg) in THF (20 mL) under Ar. After stirring overnight at 25 °C, EtOAc was slowly added (10 mL). Dilute aqueous HCl (5%, 20 mL) was carefully added, and the mixture was stirred for 1 h at room temperature. The mixture was added to water (100 mL) and extracted with ether (3 × 50 mL). The combined ether layers were washed with 5% aqueous HCl (1 × 50 mL), water (1 × 50 mL), and saturated aqueous NaCl (2 × 25 mL). The organic layer was dried over $MgSO_4$ and filtered, and the solvent was removed. The resulting oil was chromatographed on silica gel with EtOAc/hexanes (20:30) to give 0.5 g of **3c** (46% yield on starting from the allylic alcohol **17**): mp 68–70 °C; NMR ($CDCl_3$) δ 1.93 (dd, 3 H, $^3J_{AM}$ = 7 Hz; $^4J_{AX}$ = 1 Hz), 5.18 (s, 2 H), 5.25 (s, 2 H), 5.99 (dq, 1 H, $^3J_{MA}$ = 7 Hz, $^3J_{MX}$ = 16 Hz), 6.95 (s, 1 H), 7.04 (d, 1 H, J = 16 Hz), 7.25 (s, 1 H), 7.41 (m, 10 H), 10.16 (s, 1 H); mass spectrum, *m/e* 358 (M^+), 342, 281, 267.

(Isopropylamino)phenethanol Side-Chain Extension. The reported procedure[2,4] was followed closely in the synthesis of **6**, **2b**, and **2c** from the appropriate benzaldehydes **3a–c**, respectively. Only one representative example is given here.

3,4-Bis(benzyloxy)-5-(prop-2-enyl)-α,β-epoxystyrene (4b). The procedure[2,5] for the preparation of the epoxide **4b** from the aldehyde **3b** was used with the following quantities: aldehyde **3b** (1.40 g, 3.91 mmol) in dry THF (10 mL), NaH (0.2 g of a 50% oil dispersion, 4.1 mmol) in dry Me_2SO–THF (10 mL of each), and trimethylsulfonium iodide (0.8 g, 3.91 mmol) in dry Me_2SO (10 mL). After the workup, a thick oil of **4b** was obtained (1.3 g, 89.6% yield) that was relatively unstable on silica gel: NMR ($CDCl_3$) δ 2.75 (A part of ABX, q, 1 H), 3.09 (B part of ABX, t, 1 H), 3.36 (d, 2 H, J = 7.5 Hz), 3.79 (X part of ABX, t, 1 H), 4.99 (s, 2 H), 5.04 (m, 2 H), 5.13 (s, 2 H), 5.91 (m, 1 H), 6.77 (s, 2 H), 7.38 (m, 10 H). Anal. Calcd: C, 80.62; H, 6.49; O, 12.89. Found: C, 80.40; H, 6.67; O, 13.02.

1,2-Bis(benzyloxy)-4-[1-hydroxy-2-[(1-methylethyl)amino]ethyl]-6-(prop-2-enyl)benzene (5b). The epoxide **4b** (1.2 g, 3.22 mmol) was dissolved in ethanol (125 mL), and isopropylamine (20 mL) was added. The mixture was refluxed under Ar overnight and the solvent removed by rotary evaporation. The crude product was chromatographed on silica gel (40 g), giving **5b**: 0.95 g (69% yield); mp 77–78.5 °C; waxy solid; NMR ($CDCl_3$) δ 1.13 (d, 6 H, J = 6 Hz), 2.90 (m, 2 H), 3.2 (m, 1 H), 3.35 (d, 2 H, J = 7.5 Hz), 4.66 (X part of A^2X q, 1 H), 5.0 (s, 2 H), 5.06 (m, 2 H), 5.13 (s, 2 H), 5.90 (m, 1 H), 6.77 (d, 1 H, J = 1 Hz), 6.97 (d, 1 H, J = 1 Hz), 7.36 (m, 10 H); mass spectrum, *m/e* 413 ($M^+ - H_2O$), 401, 321, 267. Anal. Calcd: C, 77.93; H, 7.71; N; 3.25. Found: C, 78.03; H, 7.91; N, 3.09.

5-Propylisoproterenol Hydrochloride (2b). The benzyl ether **5b** (75 mg) was treated with aqueous HCl and extracted with CH_2Cl_2 to form the HCl salt. This substance was placed under high vacuum overnight and then dissolved in ethanol (25 mL). Pd/C (10%) was added (10 mg), and the mixture was hydrogenated under 1 atm of hydrogen at 25 °C overnight. Filtration through Celite under argon, removal of the ethanol, and lyophilization from 0.1 M HCl gave a hygroscopic, amorphous, and very air-sensitive solid, **2b** (40 mg or 87% yield), that was pure by TLC and NMR but resisted attempts at crystallization: NMR (D_2O) δ 0.92 (t, 3 H, J = 8 Hz), 1.34 (d, 6 H, J = 6 Hz), 1.60 (sextet, 2 H, J = 8 Hz), 2.60 (t, 2 H, J = 8 Hz), 3.24 (d, 2 H, J = 6 Hz), 3.48 (septet, 1 H, J = 6 Hz), 6.80 (d, 2 H, J = 1 Hz).

2-Propylisoproterenol–Phosphoric Acid. (2a). To a solution of **6** (28 mg, 0.084 mmol) in dry, distilled CH_2Cl_2 (2 mL) under nitrogen at −78 °C was added BBr_3 (85 mL, 0.89 mmol) via syringe. The reaction was allowed to warm to room temperature and stir for 19 h. The solution was then cooled to −78 °C, and the reaction was stopped by the addition of H_2O. The crude material was purified on HPLC (Whatman Magnum ODS-3; 20% MeOH, 80% 0.1 N NaH_2PO_4). The lyophilized product was then dissolved in 2 mL of MeOH and decanted from the insoluble residual NaH_2PO_4. After the MeOH solution was dried, the

product **2a** was obtained as an air-sensitive, white solid (2–3 mg, ~10% yield) that was pure by TLC and NMR: NMR (D_2O) δ 1.00 (t, 3 H), 1.44 (d, 6 H), 1.56 (m, 2 H), 2.7 (m, 2 H), 3.26 (m, 2 H), 3.54 (m, 1 H), 3.96 (m, 1 H), 6.95 (d, 1 H), 7.03 (d, 1 H).

6-(1-Acetoxyprop-2-enyl)-3,4-bis(benzyloxy)-1-(1,3-dioxolan-2-yl)benzene (19). The allylic alcohol **17** (1.8 g, 4.30 mmol) was dissolved in dry CH_2Cl_2 (40 mL), and dry pyridine (0.4 mL, 5.06 mmol), Ac_2O (0.5 mL, 5.3 mmol), and (dimethylamino)pyridine (5 mg) were added. The mixture was left in the freezer (–20 °C) overnight. Ether was added (100 mL), and the mixture was washed with 2% aqueous KOH (2 × 30 mL), 1% aqueous HCl (2 × 30 mL), and then saturated $NaHCO_3$ (3 × 30 mL). The organic phase was dried over $MgSO_4$ and filtered, and the solvent was removed. The resulting oil of **19** (after high vacuum) was produced in nearly quantitative yield: NMR ($CDCl_3$) δ 2.04 (s, 3 H), 4.04 (s, 4 H), 5.17 (m, 6 H), 5.94 (m, 1 H), 6.02 (s, 1 H), 6.56 (d, 1 H, J = 5 Hz), 6.97 (s, 1 H, 7.20 (s, 1 H), 7.40 (m, 10 H).

6-(3-Acetoxyprop-1-enyl)-3,4-bis(benzyloxy)benzaldehyde (20). The acetate **19** (1.8 g, 3.91 mmol) was dissolved in dry THF (50 mL), and dry CH_3CN (3 drops) was added. To this stirred solution under Ar was added $PdCl_2$ (20 mg). The mixture was stirred overnight at 25 °C. HCl (1 N, 20 mL) was added, and the resulting solution was stirred 1 h at 25 °C and then left overnight at –20 °C. Ether (100 mL) and water (100 mL) were added. The organic phase was separated and washed with saturated aqueous $NaHCO_3$ (3 × 25 mL), dried over $MgSO_4$, and filtered, and the solvent was removed. The oily product was chromatographed on silica gel to give **20** (1.6 g, 89% yield) as an oil: IR (neat) 2750, 1740, 1690, 1600, 1460, 1270 cm^{-1}; NMR ($CDCl_3$) δ 2.12 (s, 3 H), 4.77 (d, 2 H, J = 6 Hz), 5.23 (s, 2 H), 5.27 (s, 2 H), 6.10 (dt, 1 H, $^3J_{MX}$ = 16 Hz, $^3J_{AM}$ = 6 Hz), 7.07 (s, 1 H), 7.44 (m, 11 H), 10.18 (s, 1 H); mass spectrum, m/e 416 (M^+), 374, 373, 357, 356, 344, 343, 325, 322, 318.

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Approach to the Total Synthesis of Chlorothricolide: Synthesis of "7-*epi*-Bottom Half" and Its Union with "Top Half" Systems

Robert E. Ireland,* Wayne J. Thompson, Gabriel H. Srouji, and Rolf Etter

The Chemical Laboratories, California Institute of Technology,† Pasadena, California 91125

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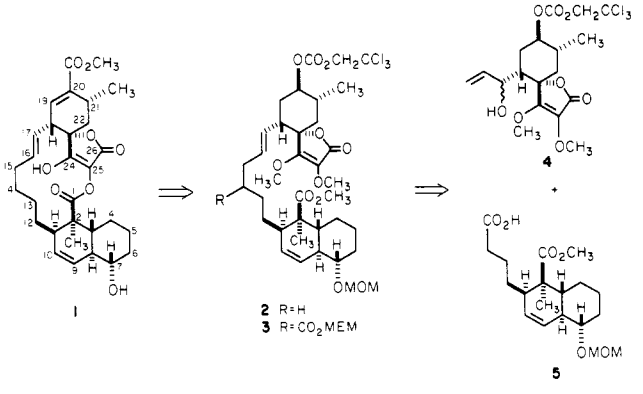
A synthesis of the "bottom half" of the antibiotic aglycon chlorothricolide (1) is described. Compound 1 was prepared in 13 steps from the readily available hydrobenzsuberone system 8; the process entails the stereoselective conjugate addition of [4-(benzyloxy)butyl]magnesium bromide to form the C ring. Union of the "top" and "bottom" halves and decarbonylation of the derived aldehyde are explored.

In a previous report[1] a basic synthetic strategy was presented for the construction of the aglycon chlorothricolide (1) from the macrolide antibiotic chlorothricin[2] (Scheme I). JO11B500##fnt# This plan entails the preparation of the open-chain ester **2** through the application of the ester enolate Claisen rearrangement[3] to the ester formed from "top half" alcohol **4** and "bottom half" acid **5** and then final lactone formation after appropriate deblocking of the ester **2**. In this earlier report[1] an efficient scheme was developed for the synthesis of the "top half" alcohol **4**, and model experiments demonstrated its utility in the proposed ester enolate Claisen rearrangement[3] approach. In the current report the construction of the "7-*epi*-bottom half" is developed, and the union of the two halves to form systems similar to the ester **2** is explored. This successful synthetic scheme stereoselectively generates a system in which the C7-hydroxyl function is epimeric with that in the natural product, but epimerization at this center is possible through oxidation and then reduction of the C7 ketone. Rather than effect this epimerization at this early stage, the "7-*epi*-bottom half" was used in subsequent explorations.

Scheme I



After investigation of several alternate routes, the sequence outlined retrosynthetically in Scheme II was pursued. In order to establish the cis relationship between the butyric acid side chain and the quaternary carboxyl group in the desired diacid **5**, we chose the oxidative cleavage of a cis-fused seven-membered ring system. This decision dictated the cis-anti-trans diol **6** as the penultimate intermediate, which itself was envisaged to arise from the tricyclic aldol-type system **7**. For the construction of this latter cis-anti-trans tricyclic system, advantage was taken of previous experience with the enedione **8**[4] which was available in large quantities by the Diels–Alder condensation of the enone **10** and the diene **11**.[5] The required

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