Total Synthesis of Milbemycin β_3

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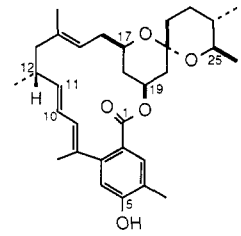
The synthesis of milbemycin β_3 (1) is described. The key features of the synthesis include (1) an acetylide addition to *trans*-5,6-dimethylvalerolactone to set up a novel hydrolysis–spirocyclization, (2) a stereoselective conjugate addition to spiroenone 6, (3) a stereoselective Wittig reaction to establish the C(14)–C(15) trisubstituted olefin, and (4) an enantioselective alkylation to establish symmetry at C(12). An intermediate previously prepared by Williams is intercepted to constitute a total synthesis.

The milbemycins are a class of structurally unique macrolides whose first members (β_1–β_3) were reported by Mishima in 1975.[2] Subsequently, 17 additional members of this class were isolated and shown to possess significant antibiotic as well as remarkable insecticidal activity.[3] Additionally, a class of closely related potent antiparasitic agents, the avermectins, were discovered by Merck in 1981.[4] The Merck program has resulted in the marketing of a semisynthetic veterinary drug, Ivermectin, which is currently being utilized on an experimental basis to treat "river blindness" in west Africa.[5]

The combination of biological activity and structural novelty of these compounds has sparked a massive effort toward their total synthesis. The first synthesis of milbemycin β_3 was reported by Smith[6] in 1982 followed shortly thereafter by the first enantioselective synthesis by Williams.[7] Since that time, numerous reports on synthetic studies on the spiroketal[8] and hexahydrobenzofuran fragments[9] of these molecules as well as additional syntheses of 1[10] have appeared. Recently, the first synthetic preparation of avermectin B_{1a} (2) was accomplished by Hanessian.[11] We disclose here a new approach to milbemycin β_3, which intersects an intermediate previously converted to 1 by Williams.[7]



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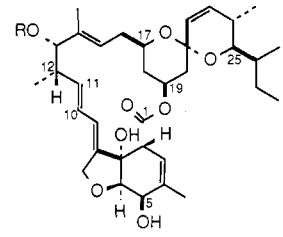

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Retrosynthetic Strategy. Retrosynthetically, we anticipated that a number of possibilities existed for the attachment of the aromatic fragment and completion of 1 if alcohol 3 was available. Thus, 3 was chosen as the key subtarget in the approach. It was felt that the remote stereogenic center at C(12) was best introduced via an asymmetric alkylation on the halide derived from allylic alcohol 4 since relative asymmetric induction at this site might prove difficult. In turn 4 could be prepared stereoselectivity from 5 by Wittig technology. On careful inspection of 5, the enone 6 arose as a logical precursor since the acetaldehyde substituent might be introduced by a conjugate addition to the unsaturated carbonyl while taking advantage of the spiroketal system as a template to control the stereochemical outcome at C(17). In a similar manner, the stereochemistry of the secondary alcohol could likely be controlled in a hydride reduction. As a result of this planning, 6 became the first important target for our synthetic venture.

Results and Discussion

A Model for Spiroketal 6. Since little was known about the preparation of systems such as 6, it was first necessary to establish a method for their synthesis to test the plausibility of the designed approach. Since Barrett[12]

(1) (a) Fellow of the Alfred P. Sloan Foundation, 1986–1988. (b) National Science Foundation Predoctoral Fellow.

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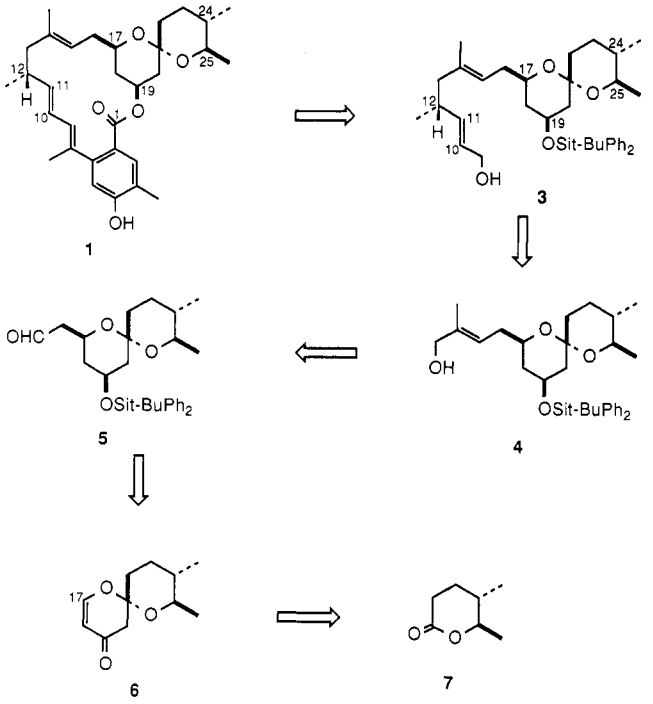
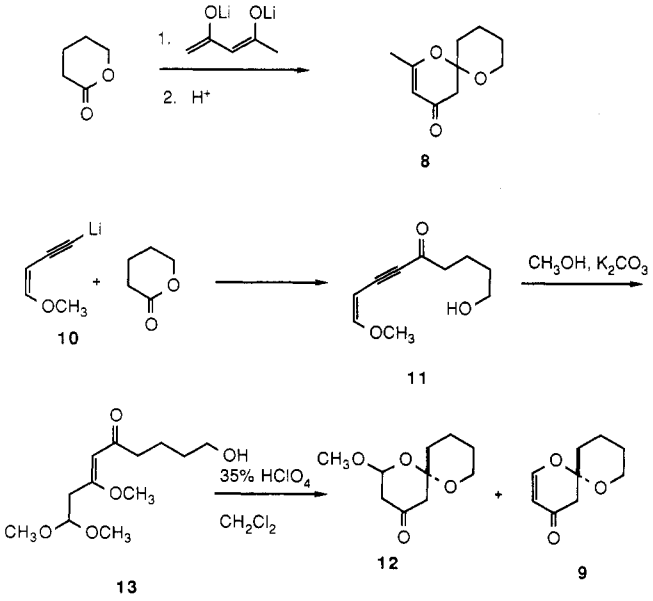


had previously prepared spiroenone **8** from valerolactone and the dianion of acetylacetone, it seemed reasonable that utilization of the dianion of formylacetone[13] might give rise to the desired model system **9**. Unfortunately, early at-



tempts to implement this strategy met with very poor results. As an alternative, we began to investigate the use of possible equivalents of formyl acetone dianion. Of the possible substitutes, the lithium acetylide **10** of 1-methoxy-1-buten-3-yne emerged as the reagent of choice. Addition of valerolactone to a THF solution of **10** at −78 °C resulted in the isolation of ketone **11** in 98% yield. We anticipated that hydration of the acetylene and hydrolysis of the enol ether of **11** would result in the spontaneous cyclization to spiroenone **9**. Of the various acids and solvent systems that were examined, the combination that gave the highest conversion and cleanest product was 35% perchloric acid in dichloromethane. These conditions were found to directly convert **11** to a 1:1 mixture of **9** and **12**.

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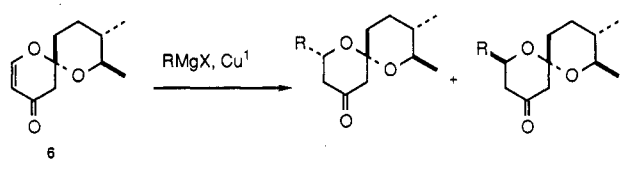
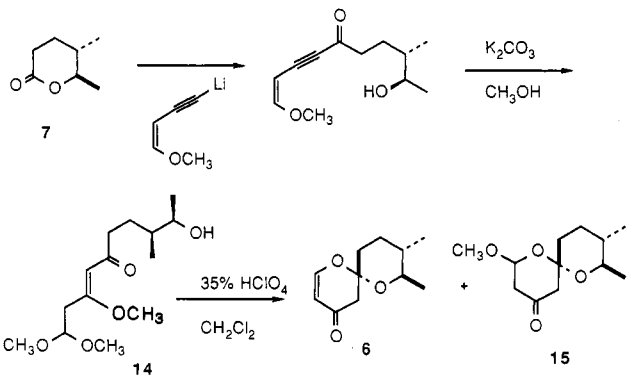
Table I



conditions	ratio
CH_2=$CHCH_2CH_2Br$,	
$[CuIBu_3P]_4$, THF	2.6:1
$[CuIBu_3P]_4$, Et_2O	1:1
CuI, THF	1.75:1
CuI, Et_2O	1:1.5
CH_2=$CHCH_2MgCl$	
$[CuIBu_3P]_4$, THF	1:3
$[CuIBu_3P]_4$, Et_2O	no reaction
CuI, THF	1:3.5
CH_2=CHMgBr,	
$[CuIBu_3P]_4$, THF	1 (**16a**):5(**16e**)
$[CuIBu_3P]_4$, Et_2O	1 (**16a**):5 (**16e**)

If the biphase was stirred more rapidly (mechanical stirrer), the desired spiroenone **9** was produced nearly exclusively in 50% yield. It was subsequently determined that higher yields could be obtained if **11** were first treated with potassium carbonate in methanol to give acetal **13** prior to the acid hydrolysis. When **13** was exposed to the 35% perchloric acid–dichloromethane biphase with rapid stirring, yields as high as 85% were obtainable.[14] With a viable route to systems such as **9** in hand, we turned our attention to the preparation of the required spiroenone **6**.

Synthesis of Spiroenone 6. Addition of lactone **7**[15] to lithium acetylide **10** followed by exposure of the product to potassium carbonate in methanol provided acetal **14** in an average overall yield of 80%. However, somewhat surprisingly, the spiroketalization under the conditions above (35% $HClO_4$, CH_2Cl_2, rapid stirring) produced spiroenone **6** in only about 10% yield. A reinvestigation



of the hydrolysis–spirocyclization conditions demonstrated that acetal **14** behaved quite differently from the unsubstituted **13**. We attributed this different behavior to an apparent difference in the water solubility of the two substances and after much experimentation determined that the optimum conditions for hydrolysis–cyclization of **14** involved addition of a dichloromethane solution of **14** to a 35% $HClO_4$–CH_2Cl_2 biphase while the biphase was irradiated with ultrasonic waves to maximize the mixing of the two phases. Under these conditions, spiroenone **6** could be obtained in 46% yield accompanied by 38% of **15**. Since attempts to reduce the amounts of **15** obtained

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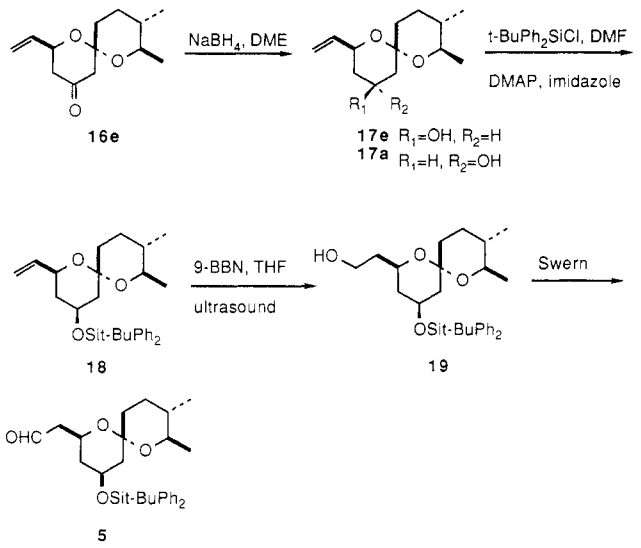
(15) Lactone **7** has been previously prepared in both racemic and optically active forms. See: ref 6, 7, and 10.

in the product mixture had failed, the possible conversion of **15** to **6** by the elimination of methanol was investigated. Treatment of **15** with various acids and bases gave traces of **6** along with a plethora of other products, but exposure of **15** to wet Amberlyst 15 (Aldrich) in refluxing dichloromethane gave the best results (51% yield). Thus, by separating the original product mixture from the hydrolysis–cyclization, and subsequent treatment of **15** as above, an overall 65% yield of **6** from **14** could be realized.

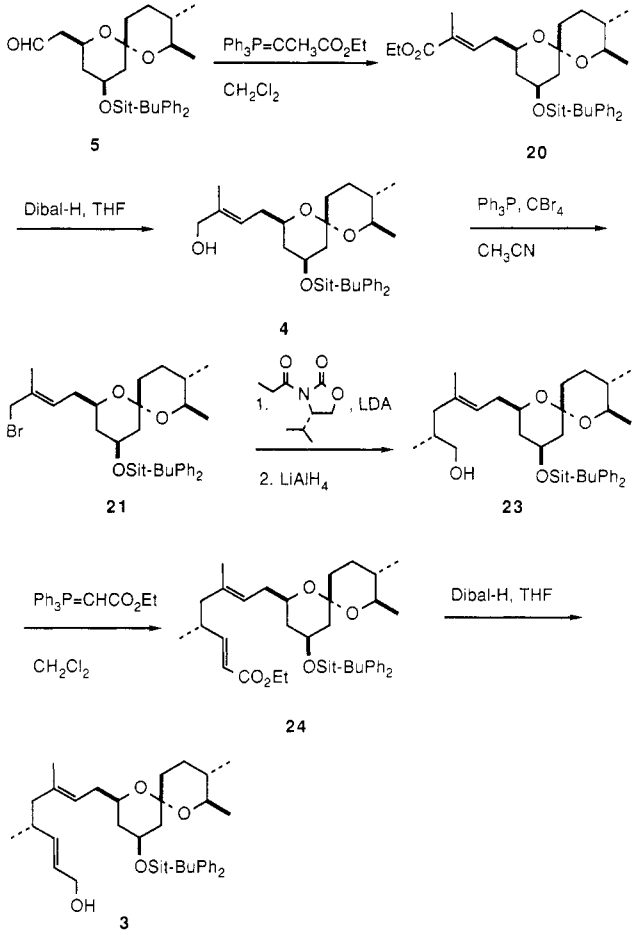
Conjugate Addition to Spiroenones: Elaboration of Spiroketal 6. With access to sufficient quantities of spiroenone **6**, we next turned our attention to the stereocontrolled introduction of a two-carbon fragment at C(17). A number of possible acetaldehyde anion equivalents for addition to **6** including allyl and vinyl organometallic reagents were envisioned. Thus, we studied the effects of solvent and organometallic reagent for several alkenyl organometallics to determine the optimum conditions for highest yield and stereoselectivity. These results are shown in Table I. The best results (60% yield, **16e**:**16a** = 5:1) were obtained by utilizing the addition of vinylmagnesium bromide catalyzed by $[Bu_3CuI]_4$[16] in diethyl ether. The two isomers were separated by flash chromatography, and the stereochemistry of **16e** was established by inspection of the coupling constants in the 250-MHz ^1H NMR spectrum. The coupling between H_{17a} and H_{18a} in **16e** was 12.5 Hz, and $J_{17a,18e}$ was 5.0 Hz, indicating an axial–axial and an axial–equatorial coupling. The stereoselectivity observed in this conjugate addition is dependent on the size of the substituent at C(25) since replacement of the C(25) methyl with an isopropyl group increases the selectivity from 5:1 to >25:1 in favor of the equatorial isomer.[17]

Reduction of ketone **16e** with sodium borohydride in dimethoxyethane gave a 3:1 mixture of readily separable alcohols **17e**:**17a** in 97% yield. The undesired isomer **17a**



could be easily recycled by Jones oxidation followed by reduction ($NaBH_4$, DME). At this point all the stereocenters were in place with the exception of the remote stereogenic center at C(12). Alcohol **17e** was protected as its *tert*-butyldiphenyl silyl ether to give **18** in 95% yield. Hydroboration of olefin **18** with borane–methyl sulfide resulted in a 70:30 mixture of the primary to secondary alcohols whereas use of 9-BBN and ultrasound gave a single alcohol **19** in quantitative yield after oxidative workup.[18] Swern oxidation[19] of **19** produced the desired aldehyde **5** (95% yield) ready for extension of the bridging chain.

Completion of the Bridging Chain: Formal Synthesis of Milbemycin β_3. With the spiroketal completed, we turned our attention to completing the bridging chain and introducing the stereocenter at C(12). Reaction of aldehyde **5** with (carbethoxyethylidene)triphenylphosphorane in dichloromethane at reflux provided ester **20** with complete control of the olefin geometry in near quantitative yield.[22] Reduction of the ester with diiso-



butylaluminum hydride in THF produced the allylic alcohol **4** in greater than 90% yield. This alcohol was readily converted to bromide **21** by the action of carbon tetrabromide and triphenylphosphine in acetonitrile.[20] These were essentially the only conditions found that would give clean conversion to the allylic bromide without scrambling the olefin geometry.

Addition of bromide **21** to an excess of the Evans chiral imide enolate **22**[21] followed immediately by reductive removal of the chiral auxiliary with lithium aluminum hydride afforded alcohol **23** in 50% overall yield. Although

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(17) Crimmins, M. T.; Hollis, W. G., Jr.; Bankaitis-Davis, D. M. *Tetrahedron Lett.* **1987**, *28*, 3651.
(18) Hydroboration of systems similar to **18** had been previously carried out with 9-BBN (see ref 11); however, we found these to be unacceptably slow. The use of ultrasound dramatically increases the rate of reaction. See: Brown, H. C.; Racherla, U. S. *Tetrahedron Lett.* **1985**, *26*, 2187.
(19) Mancuso, A. J.; Huang, S.-L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480.
(20) Hooz, J.; Gilani, S. S. H. *Can. J. Chem.* **1968**, *46*, 86.
(21) Evans, D. A.; Ennis, M. D.; Mathre, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 1737.
(22) A similar strategy has been independently developed by Baker in his synthesis of milbemycin β_3. See ref 10d.

the efficiency of this reaction might be improved by use of the allylic iodide, we chose the bromide due to our inability to prepare the iodide[22] without scrambling the olefin geometry. That the alkylation had occurred with >95% ee was evident from the 400-MHz ^{1}H NMR, which displayed a single methyl doublet for the C(12) methyl group.

Completion of the bridging chain was readily accomplished by Swern oxidation[19] followed immediately by condensation of the aldehyde with (carbethoxymethylene)triphenylphosphorane to provide ester **24** in 95% yield. Careful reduction of the ester with Dibal-H in THF at −78 °C cleanly produced 85% of alcohol **3**, which was spectrally identical with that previously prepared by Williams.[7] Since Williams[23] has previously converted **3** to milbemycin β_3, preparation of **3** constitutes a total synthesis of **1**.

Experimental Section

Addition of 10 to δ-Valerolactone: Preparation of Spiroketal 9. To a three-neck, 250-mL, round-bottom flask equipped with a nitrogen inlet tube was added a solution of freshly distilled 1-methoxy-1-buten-3-yne (2.25 g, 27.4 mmol) in 50 mL of dry THF. After the reaction mixture was cooled to −78 °C, a solution of *n*-butyllithium in hexane (2.6 M, 10.6 mL, 27.4 mmol) was added dropwise over 5 min. Stirring was continued at −78 °C for 1 h, after which a solution of δ-valerolactone (2.74 g, 27.4 mmol) in 5 mL of THF was added rapidly. The reaction mixture was stirred for 1 h at −78 °C, quenched with saturated aqueous ammonium chloride, warmed to room temperature, and diluted with ether. The organic layer was dried over magnesium sulfate, filtered, and concentrated to provide 4.89 g (98%) of keto alcohol **11** as a pale yellow oil, which was used without further purification: IR (neat) 3625, 3470, 2170, 1662, 1620, 1392, 1276 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.50–1.85 (band, 4 H), 2.61 (t, J = 6 Hz, 2 H), 2.74 (br s, 1 H), 3.63 (t, J = 6 Hz, 2 H), 3.87 (s, 3 H), 4.67 (d, J = 6.4 Hz, 1 H), 6.60 (d, J = 6.4 Hz, 1 H).

A solution of potassium carbonate (383 mg, 2.75 mmol) and keto alcohol **11** (4.89 g, 26.9 mmol) in 50 mL of methanol was stirred for 16 h whereupon the methanol was removed in vacuo. The residue was taken up in ether, filtered, dried, and concentrated to give crude acetal **13**: IR (neat) 3620, 2170, 1735, 1664, 1623 cm^{-1}; ^{1}H NMR (100 MHz, $CDCl_3$) δ 1.45–1.82 (band, 4 H), 2.50 (t, J = 6 Hz, 2 H), 2.97 (br s, 1 H), 3.22 (d, J = 6 Hz, 2 H), 3.35 (s, 6 H), 3.61 (t, J = 6 Hz, 2 H), 3.71 (s, 3 H), 4.73 (t, J = 6 Hz, 1 H), 5.55 (s, 1 H). This material was dissolved in 100 mL of dichloromethane and placed in a 500-mL round-bottom flask equipped with a mechanical stirrer. While this solution was stirred vigorously, a freshly prepared solution of 35% aqueous perchloric acid (1:1 concentrated $HClO_4$–H_2O) was poured in slowly. After being stirred for 10 min, the organic layer was neutralized with sodium bicarbonate, dried over magnesium sulfate, and concentrated to give 3.88 g (86%) of spiroketal **9** as a colorless oil accompanied by a trace of **12**. **9**: IR ($CDCl_3$) 1680, 1610, 1405, 1235 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.40–2.10 (band, 6 H), 2.57 (dd, J = 16.6 Hz, 0.5 Hz, 1 H), 2.70 (d, J = 16.6 Hz, 1 H), 3.73 (m, 2 H), 5.46 (dd, J = 6 Hz, 0.5 Hz, 1 H), 7.22 (d, J = 6 Hz, 1 H). Anal. Calcd for $C_9H_{12}O_3$: C, 64.27; H, 7.19. Found: C, 64.14; H, 7.27.

8(*R*),9(*S*)-Dimethyl-1,7-dioxaspiro[5.5]undec-2-en-4-one (6). To an oven-dried, 100-mL, round-bottom flask equipped with an addition funnel and nitrogen inlet tube was added 30 mL of dry THF and 778 mg (9.47 mmol) of freshly distilled *cis*-1-methoxy-1-buten-3-yne. The solution was cooled to −78 °C, and 3.44 mL (9.47 mmol, 2.5 M in hexane) on *n*-butyllithium was added dropwise. The solution was stirred for 30 min at −78 °C whereupon a solution of 1.1037 g (8.61 mmol) of *trans*-4(*S*),5-(*R*)-dimethylvalerolactone (**7**) in 8 mL of dry THF was added dropwise; the mixture was stirred for 1 h at −78 °C and quenched with saturated aqueous ammonium chloride. The mixture was warmed to room temperature and diluted with ether, and the organic layer was dried and concentrated to afford 1.72 g (95%) of keto alcohol, which was used without further purification.

A portion of the above material (889 mg, 4.23 mmol) and 585 mg of finely ground potassium carbonate were dissolved in 30 mL of methanol, and the mixture was stirred at room temperature for 16 h. The mixture was concentrated to about 10 mL, diluted with 50 mL of ether, and filtered through a pad of Celite. The filtrate was dried over $MgSO_4$ and concentrated to produce 987 mg (85%) of acetal **14** as a pale yellow oil: IR ($CDCl_3$) 3630, 3640, 1680, 1585, 1455 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.88 (d, J = 6.5 Hz, 3 H), 1.15 (d, J = 6.5 Hz, 3 H), 1.40–1.60 (band, 2 H), 1.79 (m, 1 H), 2.05 (br s, 1 H), 2.30–2.70 (band, 2 H), 3.12 (d, J = 6 Hz, 2 H), 3.34 (s, 6 H), 3.58 (m, 1 H), 3.68 (s, 3 H), 4.72 (t, J = 6 Hz, 1 H), 5.52 (s, 1 H).

To a 125 × 65 mm crystallizing dish suspended by a wire cage in a Branson, 125w, 13 × 24 cm ultrasonic cleaner was added 75 mL of methylene chloride and 25 mL of 35% perchloric acid. The solution was irradiated for 1 min, and to this mixture was added, dropwise, over 5 min, a solution of 987 mg (3.4 mmol) of acetal **14** in 10 mL of dichloromethane. The mixture was irradiated for 5 min after the addition was completed, the layers were separated, and the organic layer was washed with saturated sodium bicarbonate, dried over magnesium sulfate, and concentrated to give 628 mg (83%) of crude spiroketals **6** and **15** in a ratio of 1.3:1. Flash chromatography provided 319 mg (47%) of **6** and 287 mg (36%) of **15**. Spiroketal **6**: IR ($CDCl_3$) 1675, 1610, 1410, 1380, 1240 cm^{-1}; ^{1}H NMR (250 mHz, $CDCl_3$) δ 0.90 (d, J = 6.5 Hz, 3 H), 1.13 (d, J = 6.5 Hz, 3 H), 1.50–1.70 (band, 4 H), 2.04 (m, 1 H), 2.58 (dd, J = 17 Hz, 0.5 Hz, 1 H), 2.70 (d, J = 17 Hz, 1 H), 3.48 (dq, J = 6.5 Hz, 10 Hz, 1 H), 5.45 (dd, J = 5.7 Hz, 0.5 Hz, 1 H), 7.20 (d, J = 5.7 Hz, 1 H). Anal. Calcd for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22. Found: C, 67.27; H, 8.07.

Spiroketal **15**: IR ($CDCl_3$) 1730, 1450, 1380, 1310 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.89 (d, J = 6.5 Hz, 3 H), 1.13 (d, J = 6.5 Hz, 3 H), 1.50–1.85 (band, 4 H), 1.92 (dm, J = 11 Hz, 1 H), 2.48 (m, 3 H), 2.76 (dm, J = 15 Hz, 1 H), 3.47 (dq, J = 6.5 Hz, 10 Hz, 1 H), 3.55 (s, 3 H), 4.84 (dd, J = 3 Hz, 4 Hz, 1 H). Anal. Calcd for $C_{12}H_{20}O_4$: C, 63.14; H, 8.83. Found: C, 62.94; H, 8.63.

Conversion of 15 to 6. A suspension of Amberlyst 15 (enough to half fill a 100-mL round-bottom flask) in a solution of 713 mg (3.12 mmol) of spiroketal **15** in 35 mL of dichloromethane in a 100-mL round-bottom flask was heated to reflux for 16 h, cooled, filtered, and concentrated. The residue was flash chromatographed to provide 311 mg (51%) of spiroketal **6** identical with that prepared above.

2(*S*)-Vinyl-8(*R*),9(*S*)-dimethyl-1,7-dioxaspiro[5.5]undecan-4-one (16e). A 100-mL, oven-dried, three-neck, round-bottom flask equipped with a low-temperature thermometer and a nitrogen inlet tube was purged with nitrogen for 5 min and then charged with 15 mL of dry ether and 194 mg (0.49 mmol) of $[Cu^IIBu_3P]_4$. The solution was cooled to −45 to −55 °C with an acetonitrile–dry ice bath. To this cooled solution was added, dropwise, 4.94 mL (4.94 mmol) of a 1 M solution of vinylmagnesium bromide in THF while maintaining the internal temperature was maintained between −45 and −55 °C. After the mixture was stirred for 45 min at this temperature, a solution of 97 mg (0.49 mmol) of spiroketal **6** in 5 mL of dry ether was added dropwise, and the mixture was stirred for an additional 15 min and quenched with 3 mL of saturated ammonium chloride and 1 mL of ammonium hydroxide. The mixture was warmed to room temperature, and the organic layer was dried over magnesium sulfate, concentrated, and flash chromatographed to afford 55 mg (50%) of spiroketal **16e** and 12 mg (10%) of **16a**. **16e**: IR ($CDCl_3$) 1725, 1450, 1414, 1380, 1330 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.85 (d, J = 6.5 Hz, 3 H), 1.11 (d, J = 6.5 Hz, 3 H), 1.50–1.70 (band, 4 H), 1.90 (m, 1 H), 2.31 (dd, J = 15.2 Hz, 12.3 Hz, 1 H), 2.43 (s, 2 H), 2.48 (dd, J = 15.2 Hz, 5.6 Hz, 1 H), 3.28 (dq, J = 6.5 Hz, 10 Hz, 1 H), 4.35 (m, 1 H), 5.27 (m, 2 H), 5.94 (m, 1 H). Anal. Calcd for $C_{13}H_{20}O_3$: C, 69.61; H, 8.89. Found: C, 69.37; H, 9.00.

16a: IR ($CDCl_3$) 1725, 1445, 1425, 1405, 1380, 1310 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.88 (d, J = 6.5 Hz, 3 H), 1.12 (d, J = 6.5 Hz, 3 H), 1.40–1.70 (band, 4 H), 1.87 (m, 1 H), 2.45 (dd, J = 17.1 Hz, 3.9 Hz, 1 H), 2.57 (s, 2 H), 2.64 (dd, J = 17.1 Hz, 10.4 Hz, 1 H), 3.73 (dq, J = 6.5 Hz, 1 H), 4.46 (m, 1 H), 5.26 (m,

(23) We thank Professor David R. Williams for kindly providing spectra of alcohol **3** and other intermediates.

2 H), 5.95 (m, 1 H). Anal. Calcd for $C_{13}H_{20}O_3$: C, 69.61; H, 8.99. Found: C, 69.31; H, 9.18.

2(*S*)-Vinyl-4(*S*)-hydroxy-8(*R*),9(*S*)-dimethyl-1,7-dioxaspiro[5.5]undecane (17e). To a 100-mL, three-neck, round-bottom flask equipped with a nitrogen inlet tube and an addition funnel was added 22 mg (0.572 mmol) of sodium borohydride and 30 mL of dry 1,2-dimethoxyethane. This mixture was cooled to 0 °C, and 64 mg (0.286 mmol) of ketone **16e** in 5 mL of dimethoxyethane was added. Stirring was continued for 3 h whereupon the reaction was quenched by the slow addition of 10% aqueous hydrochloric acid. The dimethoxyethane was removed in vacuo, and the residue was extracted with ether. The ether layer was dried, concentrated, and chromatographed to provide 48 mg (74%) of alcohol **17e** and 14 mg (23%) of the axial isomer **17a**. **17e**: IR ($CDCl_3$) 3600, 1446, 1378, 970 cm^{-1}; ^1H NMR (250 MHz, CDC_3) δ 0.83 (d, J = 6.5 Hz, 3 H), 1.12 (d, J = 6.5 Hz, 3 H), 1.19–2.10 (band, 9 H), 3.28 (dq, J = 6.5 Hz, 10 Hz, 1 H), 4.15 (m, 1 H), 4.20 (m, 1 H), 5.20 (m, 2 H), 5.89 (m, 1 H). Anal. Calcd for $C_{13}H_{22}O_3$: C, 68.88; H, 9.80. Found: C, 68.65; H, 9.72.

17a: IR ($CDCl_3$) 3490, 1450, 1440, 1420, 1380, 1355 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.84 (d, J = 6.5 Hz, 3 H), 1.17 (d, J = 6.5 Hz, 3 H), 1.40–1.95 (band, 9 H), 3.40 (dq, J = 6.5 Hz, 10 Hz, 1 H), 4.09 (m, 1 H), 4.27 (d, J = 11 Hz, 1 H), 4.39 (m, 1 H), 5.22 (m, 2 H), 5.91 (m, 1 H). Anal. Calcd for $C_{13}H_{22}O_3$: C, 68.88; H, 9.80. Found: C, 68.65; H, 9.72.

2(*S*)-Vinyl-4(*S*)-[(*tert*-butyldiphenylsilyl)oxy]-8(*R*),9-(*S*)-dimethyl-1,7-dioxaspiro[5.5]undecane (18). A 50-mL, two-neck, round-bottom flask equipped with a nitrogen inlet tube was charged with 117 mg (0.52 mmol) of alcohol **17e** in 15 mL of *N*,*N*-dimethylformamide. To this solution was added 0.3 mL (1.03 mmol), of *tert*-butylchlorodiphenylsilane, 78 mg (1.14 mmol) of imidazole, and 13 mg (0.10 mmol) of (dimethylamino)pyridine. After being stirred for 2 days, the reaction mixture was diluted with 30 mL of 1:1 ether–water. The organic layer was washed twice with water, dried, concentrated, and flash chromatographed (10% ethyl acetate in hexanes) to afford 289 mg (97%) of **18**: IR ($CDCl_3$) 3080, 3060, 3020, 2960, 1450, 1430, 1380, 1305, 1270, 1250 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.77 (d, J = 6.5 Hz, 3 H), 0.97 (d, J = 6.5 Hz, 3 H), 1.04 (s, 9 H), 1.10–2.00 (band, 9 H), 3.12 (dq, J = 6.5 Hz, 10 Hz, 1 H), 3.80 (m, 1 H), 4.22 (m, 1 H), 5.09 (m, 2 H), 5.78 (m, 1 H), 7.38 (m, 6 H), 7.66 (m, 4 H). Anal. Calcd for $C_{29}H_{40}O_3Si$: C, 74.95; H, 8.68. Found: C, 74.54; H, 8.80.

2(*R*)-(2-Hydroxyethyl)-4(*S*)-[(*tert*-butyldiphenylsilyl)-oxy]-8(*R*),9(*S*)-dimethyl-1,7-dioxaspiro[5.5]undecane (19). A 50-mL, two-neck, round-bottom flask equipped with a nitrogen inlet tube and a reflux condenser was partially submerged in a Branson, 125w, 13 × 24 cm ultrasonic cleaner and charged with 91 mg (0.266 mmol) of olefin **18** in 30 mL of dry THF and 2.13 mL (1.07 mmol) of a 0.5 M solution of 9-BBN in THF. The mixture was irradiated for 1 h, and the entire apparatus was transferred to a magnetic stirring plate. A magnetic stir bar was added, and 1 mL of ethanol, 2 mL of 6 N NaOH, and 2 mL of 30% hydrogen peroxide was added. The mixture was stirred for 4 h, 1 g of potassium carbonate was added, and the layers were separated. The organic layer was dried, concentrated, and flash chromatographed to yield 96 mg (100%) of alcohol **19** as a clear, colorless oil: IR ($CDCl_3$) 3510, 1432, 1384, 1252, 1197, 1116, 1078, 1000 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.79 (d, J = 6.5 Hz, 3 H), 0.99 (d, J = 6.5 Hz, 3 H), 1.05 (s, 9 H), 1.10–1.98 (band, 12 H), 3.12 (dq, J = 6.5 Hz, 10 Hz, 1 H), 3.58 (br t, J = 9 Hz, 2 H), 3.73 (m, 1 H), 4.19 (m, 1 H), 7.37 (m, 6 H), 7.66 (m, 4 H). Anal. Calcd for $C_{29}H_{42}O_4Si$: C, 72.16; H, 8.77. Found: C, 71.88; H, 8.92.

Unsaturated Ester 20. To a 100-mL, three-neck, round-bottom flask equipped with two addition funnels and a nitrogen inlet tube was added 5 mL of dry dichloromethane and 0.21 mL (0.23 mmol) of a 1.15 M solution of oxalyl chloride in CH_2Cl_2. The mixture was cooled to −78 °C, whereupon 0.33 mL (0.47 mmol) of a 1.41 M solution of dimethyl sulfoxide in dichloromethane was added dropwise. After 2 min, 113 mg (0.23 mmol) of alcohol **19** in 5 mL of dichloromethane was added dropwise. Stirring was continued for 15 min, and 1.6 mL (11.7 mmol) of a 0.72 M solution of triethylamine in dichloromethane was added. After the mixture was stirred for 5 min at −78 °C, the mixture was warmed to room temperature, and 2 mL of water was added. The organic layer was washed again with water, dried over magnesium sulfate, and concentrated to provide 110 mg (98%) of aldehyde **5** as a clear, colorless oil, which was used immediately and without further purification: IR ($CDCl_3$) 1730 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.77 (d, J = 6.5 Hz, 3 H), 0.98 (d, J = 6 Hz, 3 H), 1.05 (s, 9 H), 1.10–2.00 (band, 9 H), 2.34 (ddd, J = 17.5 Hz, 2.5 Hz, 2.5 Hz, 1 H), 2.53 (ddd, J = 17.5 Hz, 10 Hz, 2.5 Hz, 1 H), 3.11 (dq, J = 6 Hz, 10 Hz, 1 H), 3.89 (m, 1 H), 4.22 (m, 1 H), 7.39 (m, 6 H), 7.65 (m, 4 H).

A solution of 58 mg (0.164 mmol) of crude aldehyde **5** and 89 mg (0.246 mmol) of (carbethoxyethylidene)triphenylphosphorane in 20 mL of dichloromethane was heated to reflux for 5 h. The reaction was cooled, the solvent was removed, and the residue was flash chromatographed to provide 66 mg (91%) of unsaturated ester **20** as a clear colorless oil: IR ($CDCl_3$) 1705, 1450, 1383, 1110 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.77 (d, J = 6.5 Hz, 3 H), 0.97 (d, J = 6.5 Hz, 3 H), 1.06 (s, 9 H), 1.10–2.00 (band, 9 H), 1.29 (t, J = 7 Hz, 3 H), 1.81 (br s, 3 H), 2.11–2.41 (band, 2 H), 3.09 (dq, J = 6.5 Hz, 10 Hz, 1 H), 3.39 (m, 1 H), 4.19 (q, J = 7 Hz, 2 H), 4.22 (m, 1 H), 6.77 (t, J = 6.5 Hz, 1 H), 7.39 (m, 6 H), 7.67 (m, 4 H). Anal. Calcd for $C_{34}H_{48}O_4Si$: C, 72.30; H, 8.57. Found: C, 72.42; H, 8.42.

Allylic Alcohol 4. To a 50-mL, three-neck, round-bottom flask equipped with an addition funnel and a nitrogen inlet tube was added 20 mL of ether and 0.54 mL (0.54 mmol) of a 1 M solution (in ether) of diisobutylaluminum hydride. The solution was cooled to −78 °C, whereupon a solution of 76 mg (0.14 mmol) of ester **20** in 5 mL of ether was added dropwise. The mixture was stirred for 1 h and quenched by the cautious addition of 10% HCl. After the mixture was warmed to room temperature, the organic layer was washed with saturated sodium bicarbonate, dried over magnesium sulfate, and concentrated to produce 69 mg (98%) of allylic alcohol **4** as a colorless oil: IR ($CDCl_3$) 3610, 1430, 1382, 1250, 1195, 1112 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.76 (d, J = 6.5 Hz, 3 H), 0.96 (d, J = 6.5 Hz, 3 H), 1.03 (s, 9 H), 1.08–2.98 (band, 9 H), 1.61 (br s, 3 H), 1.99–2.26 (band, 2 H), 3.09 (dq, J = 6.5 Hz, 10 Hz, 1 H), 3.27 (m, 1 H), 3.96 (br s, 2 H), 4.17 (m, 1 H), 5.35 (br t, J = 6.5 Hz, 1 H), 7.38 (m, 6 H), 7.66 (m, 4 H). Anal. Calcd for $C_{32}H_{46}O_3Si$: C, 73.53; H, 8.87. Found: C, 73.84; H, 8.94.

Allylic Bromide 21. Carbon tetrabromide (50 mg, 0.15 mmol) was added in small portions to a solution of 40 mg (0.076 mmol) of alcohol **4** and 40 mg (0.15 mmol) of triphenylphosphine in 20 mL of dry acetonitrile. After 15 min, the mixture was diluted with pentane, and the organic layer was washed with 10 mL of water, dried, and concentrated to afford bromide **21** as a clear, colorless oil. Flash chromatography of the crude product provided 43 mg (95%) of **21**: IR ($CDCl_3$) 1434, 1383, 1197, 1113, 1077 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.78 (d, J = 6.5 Hz, 3 H), 0.96 (d, J = 6.5 Hz, 3 H), 1.04 (s, 9 H), 1.10–1.97 (band, 9 H), 1.72 (br s, 3 H), 1.97–2.25 (band, 2 H), 3.08 (dq, J = 6.5 Hz, 10 Hz, 1 H), 3.27 (m, 1 H), 3.94 (s, 2 H), 4.16 (m, 1 H), 5.58 (dt, J = 6.5 Hz, 1 H), 7.39 (m, 6 H), 7.67 (m, 4 H). Anal. Calcd for $C_{32}H_{45}O_3BrSi$: C, 65.62; H, 7.74. Found: C, 65.89; H, 7.55.

Alcohol 23. To a cooled (0 °C) solution of 0.45 mL (3.22 mmol) of diisopropylamine in 15 mL of THF was added 1.3 mL (3.33 mmol) of a 2.5 M solution of *n*-butyllithium in hexanes. The mixture was stirred for 20 min and cooled to −78 °C, whereupon a solution of 60 mg (3.22 mmol) of chiral oxazolidone **22** in 5 mL of THF was added dropwise. The mixture was stirred for 40 min at −78 °C and warmed to 0 °C, and a solution of bromide **21** in 5 mL of dry THF was added slowly. The reaction mixture was stirred for 3 h, warmed to room temperature, and quenched with saturated aqueous ammonium chloride. The organic layer was dried over magnesium sulfate, concentrated, and chromatographed to remove any unreacted **21**. The fractions containing **22** and the crude alkylation product were concentrated, and the residue was taken up in dry ether. This solution was then added dropwise to a stirred solution of lithium aluminum hydride (76 mg, 2 mmol) in 20 mL of dry ether at room temperature. After 30 min, the reaction was carefully quenched with 10% aqueous sodium hydroxide. The salts were filtered and washed repeatedly with ether. The combined ether washes were dried, concentrated, and chromatographed to give 71 mg (50% based on recovered **21**) of alcohol **23** as a colorless oil: IR ($CDCl_3$) 3510, 1420 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.77 (d, J = 6.5 Hz, 3 H), 0.86 (d, J = 6.5 Hz, 3 H), 0.96 (d, J = 6.5 Hz, 3 H), 1.03 (s, 9 H), 1.07–2.16 (band, 13 H), 1.58 (br s, 3 H), 3.11 (dq, J = 6.5 Hz, 10 Hz, 1 H), 3.27

(m, 1 H), 3.33 (m, 2 H), 4.18 (m, 1 H), 5.15 (t, J = 6.5 Hz, 1 H), 7.38 (m, 6 H), 7.66 (m, 4 H). Anal. Calcd for $C_{35}H_{52}O_4Si$: C, 74.42; H, 9.28. Found: C, 74.17; H, 9.20.

Allylic Alcohol 3. To a 50-mL, three-neck, round-bottom flask equipped with two addition funnels and a nitrogen inlet tube was added 5 mL of dry dichloromethane and 0.03 mL (0.024 mmol) of a 0.77 M solution of oxalyl chloride in CH_2Cl_2. The mixture was cooled to -78 °C, whereupon 0.05 mL (0.048 mmol) of a 0.94 M solution of dimethylsulfoxide in dichloromethane was added dropwise. After 2 min, 13 mg (0.023 mmol) of alcohol **23** in 5 mL of dichloromethane was added dropwise. Stirring was continued for 15 min, and 0.25 mL (0.12 mmol) of a 0.48 M solution of triethylamine in dichloromethane was added. After being stirred for 5 min at -78 °C, the mixture was warmed to room temperature, and 2 mL of water was added. The organic layer was washed again with water, dried over magnesium sulfate, and concentrated to provide 12 mg (95%) of crude aldehyde, which was used immediately and without further purification. The above crude aldehyde was dissolved in 10 mL of dichloromethane along with 12 mg (0.035 mmol) of (carbethoxymethylene)triphenylphosphorane, and the mixture was heated at reflux for 2.5 h. The solvent was removed, and the residue was flash chromatographed to afford 12 mg (90%) of the unsaturated ester **24**: ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.76 (d, J = 6.5 Hz, 3 H), 0.95 (d, J = 6.5 Hz, 3 H), 0.96 (d, J = 6.5 Hz, 3 H), 1.04 (s, 9 H), 1.28 (t, J = 7 Hz, 3 H), 1.55 (br s, 3 H), 1.80–2.60 (band, 5 H), 3.10 (dq, J = 6.5 Hz, 10 Hz, 1 H), 3.24 (m, 1 H), 4.16 (m, 1 H), 4.17 (q, J = 6.5 Hz, 2 H), 5.10 (t, J = 6.5 Hz, 1 H), 5.75 (dd, J = 14.9 Hz, 1.9 Hz, 1 H), 6.90 (dd, J = 14.9 Hz, 7.5 Hz, 1 H), 7.38 (m, 6 H), 7.66 (m, 4 H).

The ester **24** was immediately reduced as follows: To a 50-mL, three-neck, round-bottom flask equipped with an addition funnel and a nitrogen inlet tube was added 10 mL of dry THF and 0.1 mL (0.1 mmol) of 1 M diisobutylaluminum hydride in hexanes. The mixture was cooled to -78 °C, and 12 mg (0.019 mmol) of ester **24** in 5 mL of THF was added dropwise. Stirring was continued for 30 min, and the reaction was quenched with 10% HCl and diluted with ether. The ether layer was dried over magnesium sulfate and concentrated to give 9 mg (80%) of allylic alcohol **3**, which was spectrally identical with that prepared by Williams: IR ($CDCl_3$) 3610, 1430 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.76 (d, J = 6.5 Hz, 3 H), 0.91 (d, J = 6.5 Hz, 3 H), 0.95 (d, J = 6.5 Hz, 3 H), 1.04 (s, 9 H), 1.10–1.75 (band, 9 H), 1.54 (br s, 3 H), 1.75–2.40 (band, 5 H), 3.11 (dq, J = 6.5 Hz, 10 Hz, 1 H), 4.17 (m, 1 H), 5.08 (t, J = 6.5 Hz, 1 H), 5.58 (m, 2 H), 7.39 (m, 6 H), 7.66 (m, 4 H).

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Empirical Correlations in Ultraviolet Spectra of Substituted Benzenes. 2. Compounds with Electron-Releasing "Parent Groups"

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The first paper[2] of this series presented an empirical procedure for estimating the position of the "primary band" in the ultraviolet absorption spectra of substituted benzenes having electron-withdrawing "parent groups". This paper extends the procedure to 424 substituted benzenes that have only electron-releasing substituents. These involve 29 electron-releasing "parent groups" and 17 of these groups serving as secondary substituents ortho, meta, or para to the parent group.

The first paper[2] of this series presented an extension of the empirical method of Scott[3] for estimating the position of the "primary band " in the ultraviolet absorption spectra of substituted benzenes having electron-withdrawing "parent groups". The present paper reports the results of applying the same purely empirical, multiple-linear-regression procedures to data on benzenes, biphenyls, and polyphenyls having only electron-releasing substituents. Again, compounds with single substituents were considered as "parent compounds" and the substituents were arranged in a priority order according to the λ_{max}'s of the parent compounds. The statistical treatment yielded empirical "base values" for the λ_{max}'s of the parent compounds and values for increments due to substituents ortho, meta, or para to the parent group. For estimation of the calculated λ_{max} of a given compound, the highest priority substituent was used as the parent group, and to the base value for that parent compound were added increments for the other substituents present.

Methods

Data. This study was based entirely on data taken from the literature.[3-6]

The "standard" solvent selected was MeOH or EtOH, but some data for aqueous solutions were used. A water-solvent correction was calculated by the same procedures used for substituent increments.

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