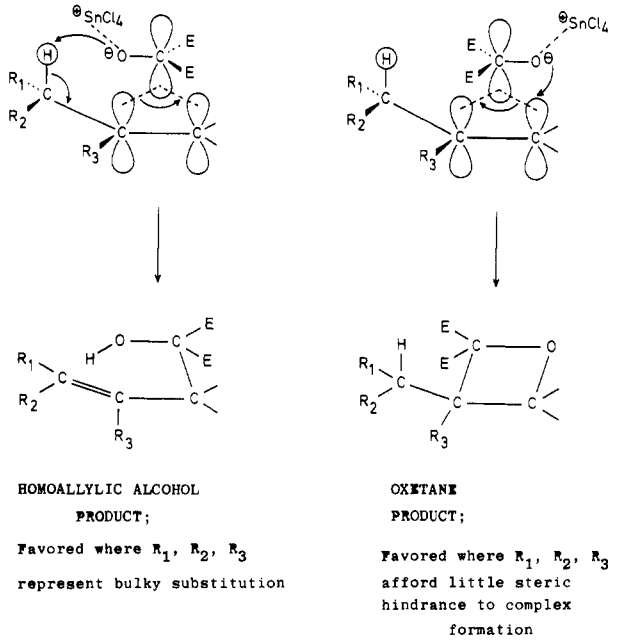
Scheme I



in the ^2H NMR, at δ 3.16. Finally, when 3-phenylpropene-*1,1-d*$_2$, **1a**, was run, the reaction product exhibited a peak at δ 4.86 in a ^2H NMR spectrum devoid of any signs of a second deuterated component like **4a** or **5a**; cf. eq 2a. These results are completely consistent with the formulation of the reaction course expressed by eq 3.

Apparently, however, $SnCl_4$ catalysis does afford a normal course of reaction of superenophiles with some ene substrates (see for example Salomon[5] and Stephenson[4]). While the formation of an oxetane byproduct has not been previously noted in the mesoxalic ester reactions,[6] (2 + 2) cycloadducts have often been observed in the purely thermal reactions of other superenophiles; e.g., the >S=N– enophiles pioneered by the Kresze school.[3,7] In fact, these observations constitute one of the lines of evidence for the requirement of a preliminary complex of the reactants as a step that organizes the subsequent rate-determining, pseudopericyclic, angular H abstraction by the nonbonding pair at the heteroatom center.

From such considerations we have arrived at the understanding that in the Lewis acid catalyzed reaction of mesoxalates (and probably, also, with other superenophiles subject to such catalysis), the rate-determining step has been shifted to the *formation* of a three-membered complex. This case is clearly identified by the low value of $k_H/k_D \approx 1.1$ observed,[4] where the normal ene reaction product (homoallyl alcohol) results from $SnCl_4$ catalysis, i.e., where R_1 and R_3 are the bulky groups phenyl and methyl, respectively. In these terms, it is a β-secondary deuterium isotope effect attributable to the recognized[8] hyperconjugative influence on the activity of the double bond in the electrophilic addition producing a three-membered intermediate complex in the rate-determining step (see Scheme I).

In summary, in the purely thermal superene reaction the TS arises from a rapidly formed, unstable (2 + 2) CT complex in which an unshielded *n* electron pair is positioned for angular abstraction of an allylic H in a concerted, pseudopericyclic process. By contrast, in the Lewis acid catalyzed mechanism the rate-determining step becomes the formation of a three-membered complex. Therein, the ease of its formation as well as its structural orientation and therefore the nature of the product-forming step are sharply affected by the substitutents on the double bond, i.e., (a) through the above-mentioned hyperconjugative influence on double bond activity in complex formation, and (b) through steric constraints stemming from repulsive interactions between the ene and enophile substituents. Scheme I depicts the alternative orbital interactions involved and the structural orientations of the complexes that can form as a result of rate-determining attack on the ene double bond by the carbonyl carbon (of the enophile) made strongly electrophilic by preliminary reaction with the $SnCl_4$ catalyst.

Acknowledgment. This work was supported by the National Science Foundation under Grant CHE 7911110. The opportunity of an Alexander von Humboldt Stiftung Senior U.S. Scientist award (to H.K.) during preparation of this manuscript in the laboratories of Professor G. Kresze at the Technical University of München is gratefully acknowledged as well.

Registry No. 1, 300-57-2; 2, 609-09-6; 6, 83762-92-9; $SnCl_4$, 7646-78-8.

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Received October 15, 1982

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(7) See also, Hori, T.; Singer, S. P.; Sharpless, K. B. *J. Org. Chem.* **1978**, *43*, 1956.
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A Stereoselective Approach to Steroid Trans C/D Ring Synthons

Summary: A stereoselective approach to the vitamin D skeleton that controls the stereochemistry at C_{13}, C_{14}, C_{17}, and C_{20} is described.

Sir: The discovery of highly active metabolites of vitamin D[1] has spurred renewed interest in synthetic studies that attack the two classic problems in steroid synthesis: (1) preparation of the C/D *trans*-hydrindan ring system[2,3] and (2) the stereospecific construction of side chain stereochemistry (at C_{20}). In particular, several papers have recently appeared[3-6] that apply the intramolecular Diels–Alder to the synthesis of angularly methylated hydrindan systems. With two exceptions, most examples give >50% cis ring fusion.[4] For several years we have been interested

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(2) Lythgoe, B.; Waterhouse, I. *J. Chem. Soc., Perkin Trans. 1* **1980**, 1405 and references cited.
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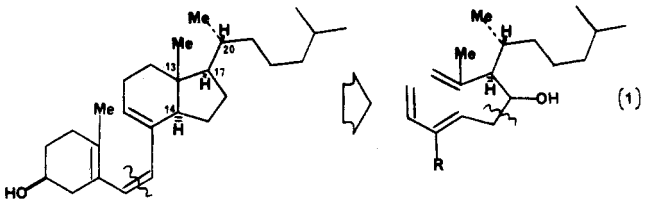
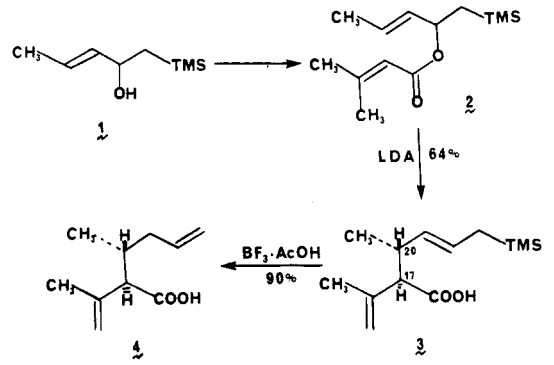
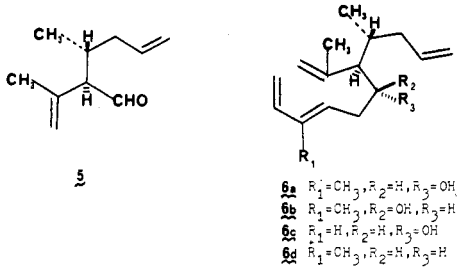
in synthetic applications of a unique "bisannelation" strategy[7a,b] involving pentadienyl anions. Application of this disconnection to precalciferol is shown in eq 1.



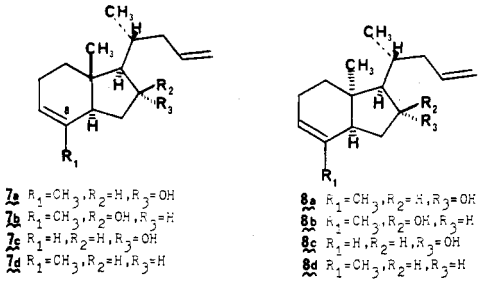
We now report our *highly convergent* approach to the vitamin D skeleton that controls the stereochemistry at C_{13}, C_{14}, C_{17}, and C_{20}. The key steroid synthon **4** is available via a "homo-Claisen"[8,9] rearrangement. Ester



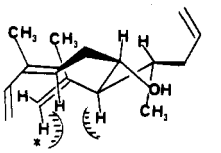
2[10] can be rearranged as described in ref 9 to acid **3** (mp 72 °C). ^{13}C NMR of the crude acid **3** showed as expected[8] at least an 8:1 ratio in favor of the desired acid **3**. Recrystallization (hexane) gave 99% purity of acid **3** (mp 72 °C) with the correct relative configuration at C_{17} and C_{20}. Protodesilylation[9] leads to acid **4** (mp 36–37 °C, 90% yield). Conversion of **4** into aldehyde **5** ($LiAlH_4$/PCC) and



addition of 3-MPL[7b] [(3-methylpentadienyl)lithium] at −78 °C (25% HMPA/THF, 50% yield) gave a 72:28 ratio of epimers **6a,b**. These isomers could be separated by silica gel chromatography and the major isomer cyclized. Thermolysis at 160 °C (20 h) gave **7a** and **8a**[13] in 3:1 ratio (78%). The β stereochemistry of the side chain was based

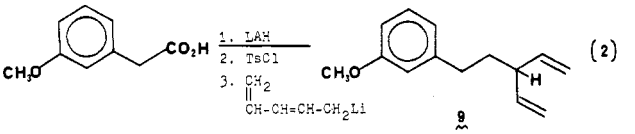


on a related study of Parker[3] and is probably the result of $A_{1,3}$ interaction with the vinylic hydrogen shown below.[11]

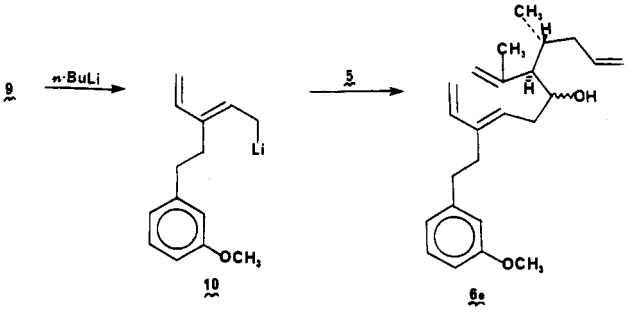


Trans-fused alcohol **7a** shows the angular methyl at δ 0.71 in the NMR spectrum, whereas the minor isomer shows an angular methyl at δ 0.93.[14] Compounds **6c** and **6d** were also prepared. Cyclization of **6c** gave 1:1 **7c/8c**, whereas cyclization of **6d** produced again a 3:1 ratio of **7d/8d**. Thus, it seems that a substituent at C_8 (i.e., R_1) is critical for trans selectivity.[15]

The synthesis of the skeleton of vitamin D proceeds as follows: 2-(Methoxyphenyl)acetic acid is converted (eq 2)



to compound **9** (57% overall).[16] When **9** is metalated, anion **10** is produced, which reacts with aldehyde **5** to produce **6e**[17] (32%, isomers at C_{16}). Cyclization of **10e** (160



°C, 20 h, 96%) followed by Jones oxidation yields ketone

(7) (a) Wilson, S. R.; Misra, R. N. *J. Org. Chem.* **1980**, *45*, 5079–5081 and references cited. (b) Wilson, S. R.; Mao, D. T. *J. Am. Chem. Soc.* **1978**, *100*, 6289–6291.

(8) Cf. Wilson, S. R.; Myers, R. S. *J. Org. Chem.* **1975**, *40*, 3309–3311.

(9) Wilson, S. R.; Price, M. F. *J. Am. Chem. Soc.* **1982**, *104*, 1124–1126.

(10) All new compounds possessed spectral and analytical data in accord with their structures.

(11) Although Parker[3] attributes the β orientation to "crowding with the chain linking the diene and dienophile", we feel that the diastereoface selectivity studied by Kozikowski[12] in intramolecular nitrone cycloadditions is likely responsible.

(12) Kozikowski, A. P.; Chen, Y. Y. *Tetrahedron Lett.* **1982**, 2081–2084.

(13) Compounds **7a/8a** showed the following: IR 2.86, 3.32, 6.10, 6.98 (br), 7.32, 9.66, 10.16, 11.12 μm; NMR δ 5.98–5.80 (m, 1 H), 5.45–5.24 (m, 1 H), 5.12–5.01 (m, 2 H), 4.16–4.00 (m, 1 H), 1.27 (s, 3 H), 0.99 (d, J = 4 Hz, 3 H), 0.93 (s, $^3/_4$ H), 0.71 (s, $^9/_4$ H); MS, *m/e* (% base) 234 (2), 147 (20), 145 (56), 119 (36), 107 (100), 106 (57), 105 (37), 95 (20), 93 (35), 91 (39), 81 (26), 79 (26), 69 (22), 67 (24), 41 (69); GC (Carbowax 20M, 25 m × 0.2mm; 140–170 °C at 2.5 °C/min), two isomers at 17.7 (25%) and 19.3 min (75%).

(14) Jackman, L. M.; Sternhall, S. "Applications of Nuclear Magnetic Resonance in Organic Chemistry", 2nd ed.; Pergamon Press: Elmsford, NY, 1972; pp 241–245.

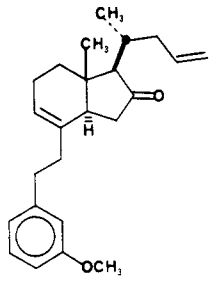
(15) See another example where a similar substituent on the diene favors *trans*-hydrindan stereochemistry: Ichihara, A.; Kimura, R.; Yamada, S.; Sakamura, S. *J. Am. Chem. Soc.* **1980**, *102*, 6353–6355.

(16) Compound **9** showed the following: IR 3.24, 3.4, 3.48, 5.48 (w), 6.1, 6.2, 6.3, 6.72, 6.84, 6.9, 6.98, 7.95 (s), 8.6, 8.72, 9.6 (br), 10.1, 10.95 (br) μm; NMR δ 7.18–6.95 (m, 1 H), 6.8–6.55 (m, 3 H), 5.66 (ddd, J = 18, 10, 7 Hz, 2 H), 5.2–4.78 (m, 4 H), 3.75 (s, 3 H), 2.85–2.4 (m, 4 H), 1.9–1.5 (m, 2 H); MS, *m/e* (% base) 202 (24), 187 (27), 173 (17), 134 (19), 122 (100), 121 (74), 105 (18), 91 (44), 77 (23).

(17) Compound **6e** showed the following: IR 2.85, 3.30, 3.36, 6.08, 6.22, 6.72, 6.90, 8.00, 8.72, 9.64, 10.15, 11.30 μm; NMR δ 7.20–6.95 (m, 1 H), 6.81–6.58 (m, 3 H), 6.28 (dd, J = 18, 10 Hz, 1 H), 5.52 (br t, J = 7 Hz, 1 H), 5.34–4.55 (m, 7 H), 3.75 (s, 3 H), 1.68 (s, 3 H), 0.90 (d, J = 5 Hz, 3 H); MS, *m/e* (% base) (M^+ = 354, not observed), 336 (1), 295 (3), 202 (24), 187 (32), 186 (30), 153 (13), 122 (47), 121 (100), 91 (37), 69 (26).

(18) Compound **11** showed the following: IR 5.75, 6.24, 6.32, 6.73, 6.92, 8.00, 8.74, 9.60 μm; NMR δ 7.26–7.00 (m 1 H), 6.80–6.58 (m, 3 H), 5.80–5.28 (m, 2 H), 5.14–4.76 (m, 2 H), 3.80 (s, 3 H, 1.08 (d, J = 6 Hz, 3 H), 0.85 (s, 3 H); MS, *m/e* (% base) 352 (5), 337 (5), 284 (11), 269 (40), 227 (38), 173 (18), 135 (21), 122 (42), 121 (100), 91 (54), 69 (37).

11 (68%, 4:1 trans/cis). The conversion of 11 into fully



11

elaborated steroids is currently in progress.

Acknowledgment. NMR spectra were obtained with the 7 T spectrometer at the Rockefeller University (purchased in part with funds from the NSF and the Camille and Henry Dreyfus Foundation. We also thank Dr. Brian Willis (Fritsche, Dodge and Olcott, NY) for NMR spectra.

Registry No. **2**, 83845-86-7; **3**, 83845-87-8; **4**, 83845-88-9; **5**, 83845-89-0; **6a**, 83845-90-3; **6b**, 83915-74-6; **6c**, 83845-91-4; **6d**, 83845-92-5; **6e** (isomer 1), 83845-93-6; **6e** (isomer 2), 83915-75-7; **7a**, 83845-94-7; **7c**, 83845-95-8; **7d**, 83845-96-9; **8a**, 83845-97-0; **8c**, 83845-98-1; **8d**, 83845-99-2; **9**, 83846-00-8; **10**, 83846-01-9; **11** (isomer 1), 83861-70-5; **11** (isomer 2), 83861-71-6; 3-MPL, 51852-87-0; 3-methoxybenzeneacetic acid, 1798-09-0.

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Structure of a New Antifungal Antibiotic, Irumamycin

Summary: The structure of irumamycin, a new antifungal antibiotic, was determined by chemical degradation, NMR spectroscopy, and ^{13}C-enriched irumamycin.

Sir: Recently, novel macrocyclic lactone antibiotics possessing various biological activities have been isolated from the metabolites of *Streptomyces*. In the course of screening for antifungal substances, a new macrolide antibiotic, irumamycin[1] (**1**), mp 95–97 °C, $[\alpha]^{25}_D$ +12° (*c* 1, $CHCl_3$), $C_{41}H_{65}NO_{12}$, was found in the culture broth of *Streptomyces subflavus* subsp. *irumaensis* nov. subsp. AM-3603.

We now report complete structural analysis of **1** by means of feeding experiments using ^{13}C-labeled precursors, chemical degradation, and 400-MHz ^1H NMR spectroscopy. Irumamycin belongs to a group of macrolide antibiotics that include venturicidin,[2] concanamycin,[3] oligomycin,[4] cytovaricin,[5] etc. and appears to be the first practical agricultural antifungal drug.

The ^{13}C NMR spectral data [ketone carbonyl (δ 211.5), lactone carbonyl (δ 173.8), carbamoyl (δ 158.1) and six olefinic carbons, an anomeric (δ 98.7) and a ketal carbon (δ 94.4), nine carbons bonded to oxygen, two of which (δ 66.4 and 64.6) are due to an epoxide, four methines, eight methylenes, and nine methyls] suggested that the antibiotic possesses a polyketide skeleton derived biosynthetically from malonate, methylmalonate, and a sugar. Acetylation of **1** with Ac_2O in pyridine afforded a diacetate **2**, mp 105–106 °C, $[\alpha]^{20}_D$ +59.4° (*c* 0.6, CH_3OH), IR (CCl_4) ν_{OH} 3450 cm^{-1} and ν_{CO} 1710–1730 cm^{-1}, ^1H NMR ($CDCl_3$) δ 2.05 and 2.10 ($OCOCH_3$), suggesting the presence of two secondary hydroxyl groups and a ketalic hydroxyl in **1**. Hydrogenation of **1** over Pd–C afforded the hexahydro derivative; this indicated the presence of three double bonds. Methanolysis of **1** gave a crystalline sugar **3**, mp 108–109 °C, $[\alpha]^{22}_D$ +92° (*c* 0.6, CH_3OH), ^{13}C NMR ($CDCl_3$) δ 158.2 ($OCONH_2$) and 98.9 (J_{CH} = 166.8 Hz, assignable to an α-anomeric carbon).[6] The ^1H NMR spectral data [δ 5.10, H-3′ ($J_{2'a,3'}$ = 11.7 and $J_{2'e,3'}$ = 5.4 Hz), δ 4.70, H-4′ ($J_{3',4'}$ = 9.2 nd $J_{4',5'}$ = 9.5 Hz)] of the monoacetate **4**, mp 107–108 °C, $C_8H_{15}NO_5$ (M^+ *m/z* 247), established the structure of **3** as methyl 3-*O*-carbamoyl-2-deoxy-α-D-rhamnoside by comparison with the NMR spectrum of the corresponding 4-*O*-carbamoyl derivative from concanamycin.[3]

Ozonolysis of **2** followed by treatment with 30% H_2O_2–concentrated HCl and then with diazomethane afforded the trichloro compound **5** as the main product, $[\alpha]^{22}_D$ +0.3° (*c* 0.6, CH_3OH). Anal. Calcd for $C_{23}H_{37}O_8Cl_3$: C, 50.41; H, 6.76; Cl, 19.45. Found: C, 50.24; H, 6.79; Cl, 19.21. The ^{13}C NMR spectrum revealed that **5** is a methyl ester of a C_{13} fatty acid possessing a ketone carbonyl (δ_C 208.9), two acetoxyl (δ_C 170.5 and 165.0), a secondary hydroxyl methylene (δ_C 74.7), and five other methyl groups. The ^{13}C chemical shift of the ester carbonyl (δ_C 165.0) as well as the proton signal at δ_H 5.90 (1 H, s) due to the hydrogen bonded to a chlorinated carbon (δ_C 65.3) indicates the presence of a dichloroacetoxy group which, as in the case of venturicidin A,[2] was produced by chlorination (HCl–H_2O_2) and decarboxylation of a malonate moiety formed by ozonolysis and H_2O_2 oxidation of **2**. Acetylation of **5** with Ac_2O in pyridine afforded the diacetate **6**, $C_{25}H_{39}O_9Cl_3$, ^1H NMR ($CDCl_3$) δ 2.05 and 2.12 ($OCOCH_3$). This indicated that **5** contains a newly generated hydroxyl group. Introduction of this hydroxyl group and the third chlorine atom of **5** resulted from epoxide ring opening with concentrated HCl after ozonolysis. In the ^{13}C NMR spectrum of **6**, a high-field shift of the signals for a methylene (δ_C 35.7, Δ 1.4 ppm) and a ketone carbonyl (δ_C 207.8, Δ 2.1 ppm) compared with those in **5** suggested that both of these are located γ to the new acetate in **6**. Treatment of **5** with zinc in acetic acid gave an oily monochloro compound **7**: $[\alpha]^{22}_D$ +2.5° (*c* 0.6, CH_3OH); $C_{23}H_{37}O_7Cl$ (M^+ *m/z* 460); UV (EtOH) λ_{max} 235 nm (log ε 4.01) (α,β-unsaturated ketone); IR (CCl_4) ν_{CO} 1670 cm^{-1}; ^1H NMR δ 6.36 (1 H, d, *J* = 9.0 Hz, olefinic proton), 1.77 (CH_3C=). Consequently the epoxide ring in **1** must be located adjacent to the ketone carbonyl. The structure of **5** was clearly shown to be 3-(acetyloxy)-10-chloro-5-[(dichloroacetyl)oxy]-9-hydroxy-11-oxo-2,4,6,8,10-pentamethyltridecanoic acid methyl ester, by careful proton spin decoupling experiments on compounds **5** and **6**, as shown in Chart I.

Homonuclear proton spin decoupling of **1** at 400 MHz indicated that a methylene group (C-12, δ 1.49, 1.68) and

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