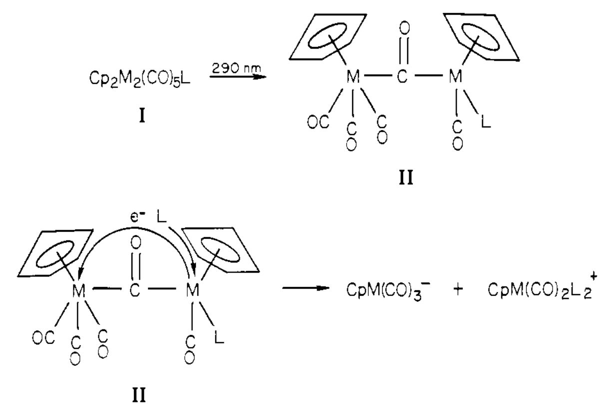
Scheme III



benzene; substitution of $(MeCp)_2Mo_2(CO)_6$ by PPh_3 ($[PPh_3]$ = 0.018 M, cyclohexane solution) at 290 nm has a quantum yield of 0.35 ± 0.04. The two lowest energy electronic absorption bands at approximately 500 and 380 nm in the $Cp_2M_2(CO)_5L$ complexes have been assigned to the $d\pi \rightarrow \sigma^*$ and $\sigma \rightarrow \sigma^*$ transitions, respectively.[2g] Because electronic excitation at 505, 435, 405, and 366 nm does not lead to disproportionation, we must conclude that these excited states are inactive toward disproportionation. The dependence of the disproportionation reaction on wavelength is independent of the ligand. Wavelength results similar to those obtained with PPh_3 were also found for the other ligands used in our study.

Homolytic cleavage of the metal–metal bond occurs upon $\sigma \rightarrow \sigma^*$ or $d\pi \rightarrow \sigma^*$ excitation of the $Cp_2M_2(CO)_5L$ complexes.[10] Therefore, the wavelength dependence of the disproportionation reaction has an important mechanistic implication: homolytic cleavage of the metal–metal bond is not sufficient to induce disproportionation. Consequently, the outer-sphere electron-transfer pathway in Scheme I and the radical-chain pathway[11] of Scheme II are not responsible for disproportionation of the $Cp_2M_2(CO)_6$ complexes. In addition, the previously proposed substitution-induced outer-sphere electron-transfer mechanism can also be eliminated from consideration.[12]

The results above suggest that disproportionation results from excitation to an excited state that is higher in energy than the $d\pi \rightarrow \sigma^*$ or $\sigma \rightarrow \sigma^*$ states. A possible pathway is outlined in Scheme III. In this scheme, the effect of 290-nm excitation is to produce intermediate II, a species with no metal–metal bond but a CO bridge. One of the metal atoms in II is coordinatively unsaturated and it undergoes nucleophilic attack by ligand L. This addition of another ligand to the metal puts sufficient electron density[13] on the metal so as to induce an inner-sphere electron transfer. Note that reaction intermediates similar to II have been proposed before in the reactions of binuclear metal carbonyl complexes.[14–16]

The quantum yield data support our suggestion that a coordinatively unsaturated intermediate such as II forms upon 290-nm excitation of the $Cp_2M_2(CO)_5L$ complexes. Note that the quantum yields for substitution of $Cp_2Mo_2(CO)_6$ and disproportionation of $Cp_2Mo_2(CO)_5L$ at 290 nm are identical within experimental error (0.35 ± 0.04 and 0.40 ± 0.04, respectively). This constant value suggests that structurally related intermediates form with constant quantum efficiency when the $Cp_2M_2(CO)_6$ and $Cp_2M_2(CO)_5L$ complexes are irradiated at 290 nm; we suggest that the M–CO–M bridged intermediate is common to both the substitution and disproportionation reactions at 290 nm. When $Cp_2M_2(CO)_6$ is irradiated, attack of L on the intermediate simply leads to substitution. When $Cp_2M_2(CO)_5L$ is irradiated, the bridged intermediate forms with the same quantum efficiency as when $Cp_2M_2(CO)_6$ is irradiated. This time, however, coordination of L (two L's are now coordinated to the same metal) polarizes the M–CO–M unit enough so as to induce electron transfer.[17] Attempts to stabilize II by irradiating $Cp_2M_2(CO)_5L$ in low-temperature glasses are in our laboratory.

Acknowledgment. We thank Professors H. B. Gray, T. L. Brown, and M. S. Wrighton for helpful discussions. S. Brawner McCullen is thanked for sending us a preprint of ref 11. Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, and to the Research Corp. for the support of this research.

Registry No. $Cp_2Mo_2(CO)_6$, 12091-64-4; $Cp_2Cr_2(CO)_6$, 12194-12-6; $Cp_2W_2(CO)_6$, 12566-66-4; $Cp_2Mo_2(CO)_5(PPh_3)$, 12119-01-6; $(MeCp)_2Mo_2(CO)_6$, 33056-03-0; PPh_3, 603-35-0; NEt_3, 121-44-8; CH_3CN, 75-05-8; $AsPh_3$, 603-32-7; $P(O\text{-}i\text{-}C_3H_7)_3$, 116-17-6; $P(OCH_3)_3$, 121-45-9; pyridine, 110-86-1; aniline, 62-53-3.

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(10) Our results indicate that homolytic cleavage of the metal–metal bond occurs with low-energy excitation of $Cp_2Mo_2(CO)_5(PPh_3)$. Irradiation (405 nm) of this complex in CCl_4 solution yields $CpMo(CO)_3Cl$ and $CpMo(CO)_2(PPh_3)Cl$. These products were identified by infrared spectroscopy. (See: Burkett, A. R.; Meyer, T. J.; Whitten, D. G. *J. Organomet. Chem.* **1974**, *67*, 67–73.) In addition, irradiation (405 nm) of $Cp_2Mo_2(CO)_5(PPh_3)$ in benzene solution gives $Cp_2Mo_2(CO)_6$. No CO stretching bands attributable to other products were observed in the infrared spectrum. The products of the Cl atom abstraction reaction and the cross-coupling reaction are consistent with initial homolytic cleavage of the metal–metal bond.

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(13) The electron-donating ability of the entering ligand is the key to whether a particular ligand can induce disproportionation or whether just substitution occurs. This aspect of the mechanism will be discussed in a full paper.

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(17) Although the quantum yield data are consistent with the formation of intermediate II in Scheme III, our results cannot rule out direct heterolysis of the M–M bond at 290 nm. The $\sigma\sigma^*$ singlet excited state of a metal–metal bonded complex is a bound ionic state. Irradiation at 290 nm may excite the molecule to a vibrational energy level of the $\sigma\sigma^*$ singlet state that is above the dissociation limit and ions may result.

Stereoselective Total Synthesis of 1α,25-Dihydroxycholecalciferol

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Received December 23, 1981

The isolation and structure determination of the physiologically active vitamin D_3 metabolite 1α,25-dihydroxycholecalciferol (**1**)[1] and its use as a lifesaving drug for osteodystrophy due to renal failure have stimulated significant efforts toward synthesis of this natural product.[2] We report here the first[3] total and chiral synthesis of 1α,25-dihydroxycholecalciferol, which can also be used efficiently in the preparation of other 1α-hydroxy vitamin D metabolites.

Lythgoe and co-workers have shown[4,5] that the lithium phos-

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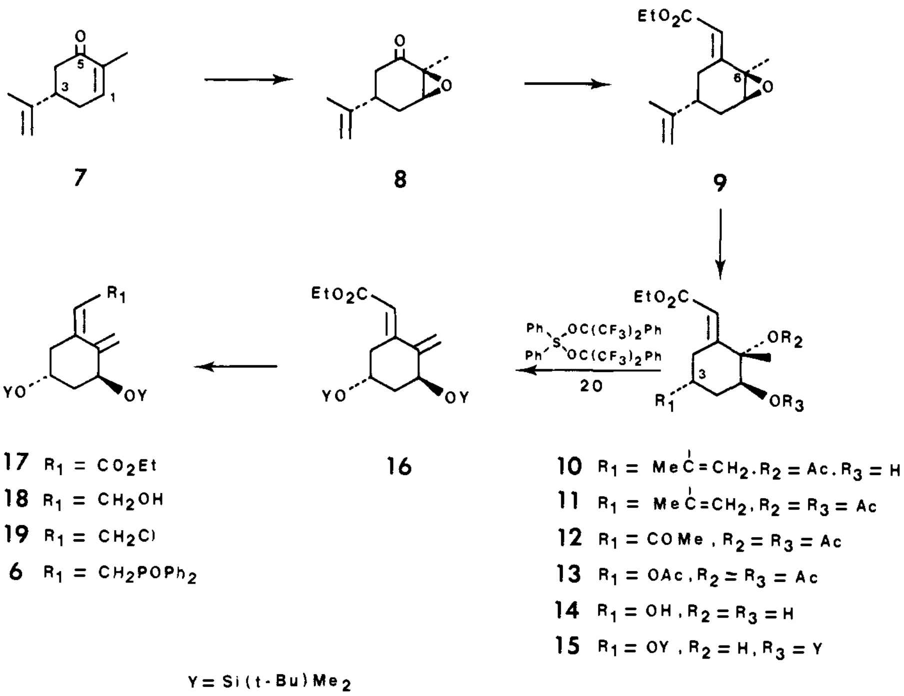
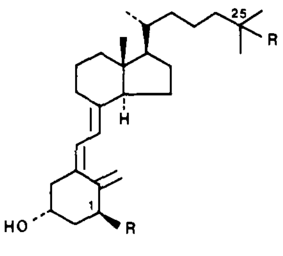
(3) This synthesis was first presented by us (E.G.B.) at the Gordon Conference on Natural Products, July, 1981.

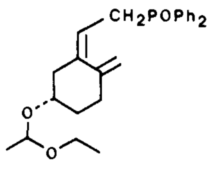
Scheme I



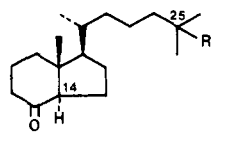


1 R = OH

2 R = H

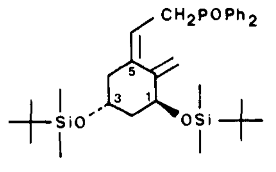


3



4 R = H

5 R = OH



6

phinoxy carbanion derived from **3** condenses with the Windaus and Grundmann ketone **4**[6] to give directly cholecalciferol (**2**). We anticipated, therefore, that the carbanion of the analogous 1α-hydroxylated phosphine oxide **6**[7] should react in similar fashion with the 25-hydroxy ketone **5** to give the desired 1α,25-dihydroxy metabolite **1**.

d-Carvone (**7**)[8] (Scheme I) was selected as the starting material in the synthesis of the ring A precursor **6**. Our synthesis plan called for the stereocontrolled formation of the additional chiral center at C-1,[7] oxidative degradation of the isopropenyl side chain at C-3 with retention of configuration, and the establishment of the two-carbon appendage at C-5, with the exocyclic *Z* double bond.

Formation of the C-1 chiral center was provided by known stereospecific epoxidation of *d*-carvone.[9] Horner–Emmons reaction of the carvone epoxide **8** with the carbanion of diethyl (carboxyethyl)phosphonate[10] (THF, 25 °C) gave a 9:1 mixture of the 5*E* unsaturated ester **9** and its 5*Z* isomer, which were separated by chromatography on silica. The desired major isomer **9**, obtained in 87% yield, was then treated with sodium acetate in acetic acid (50 °C). Under these conditions, the epoxide ring underwent regiospecific cleavage[11] to give the *trans*-hydroxyacetate **10**[12] (80% yield), the structure of which was easily assigned by NMR.[13] Acetylation (Ac_2O/pyridine, 25 °C) gave the diacetate **11** (96% yield), which was smoothly converted to the methyl ketone **12** (KIO_4/OsO_4, THF/H_2O, 25 °C) and finally to the triacetate **13** (CF_3CO_3H, NaH_2PO_4, CH_2Cl_2, 0 °C, 75% yield from **11**). Saponification with sodium ethoxide in ethanol gave not only the expected triol **14**[14] but also large amounts of a byproduct resulting from elimination of the 3-acetoxy group. To avoid this loss, a sequence of mild acidic hydrolysis (H^+ cation-exchange resin,[15] EtOH, 50 °C) and base treatment (EtONa, EtOH, 25 °C, 85% overall yield) was carried out instead. The stereochemical assignments made thus far were confirmed by a complete three-dimensional X-ray single-crystal analysis of the triol **14**, which

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(7) Steroidal numbering is used.

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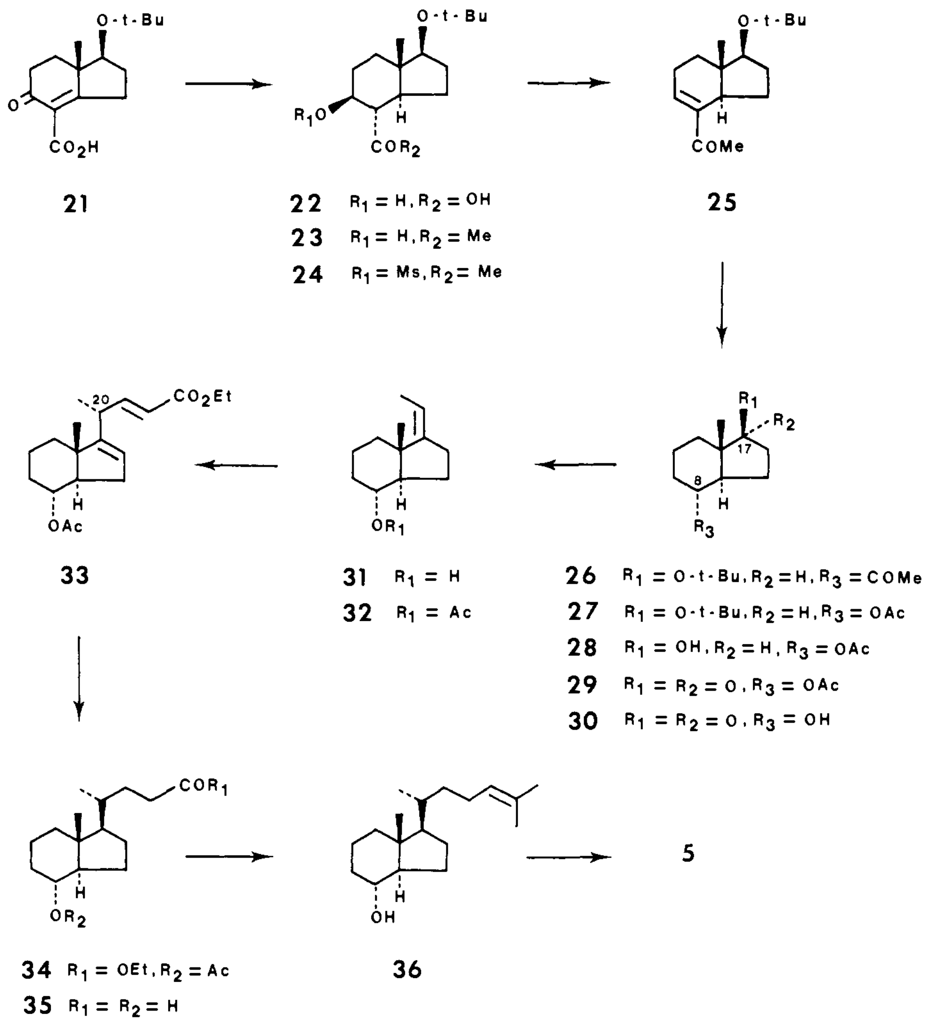
(12) NMR ($CDCl_3$) δ 1.28 (3 H, t, *J* = 7.2 Hz), 1.68 (3 H, s), 1.76 (3 H, br s), 2.03 (3 H, s), 3.80 (1 H, br d, *J* = 13.0 Hz), 4.06 (1 H, br m), 4.17 (2 H, q, *J* = 7.2 Hz), 4.78 (2 H, br s), 5.89 (1 H, s).

(13) Treatment of the minor 5*Z* isomeric epoxide, under the same conditions (NaOAc, AcOH), gave approximately a 1:1 mixture of regioisomeric hydroxyacetates. We ascribe this lack of regioselectivity to the sterical crowding brought about by the carbethoxy group, which hinders the attack in position 6 by the nucleophile.

(14) **14**: mp 95–96 °C; $[\alpha]^{25}_{D}$ +76.6 (*c* 0.5, EtOH); NMR ($CDCl_3$) δ 1.29 (3 H, t, *J* = 7.20 Hz), 1.32 (3 H, s), 3.91 (1 H, br d, *J* = 14.0 Hz), 3.98 (1 H, br s), 4.17 (2 H, q, *J* = 7.20 Hz), 4.24 (1 H, br s), 6.30 (1 H, br s).

(15) AG 50W-X4 Bio-Rad Laboratories, Richmond, CA 94804.

Scheme II



was then selectively bissilylated[16] to **15** [(t-Bu)(Me)$_2$SiCl, imidazole, DMF, 25 °C, 95% yield].

It was anticipated that, under the conditions of an E$_2$ elimination, the tertiary hydroxy group of **15** would preferentially give an exocyclic double bond. However, treatment of **15** with thionyl chloride or phosphorus oxychloride in pyridine, as well as with several other dehydrating agents, gave only complex mixtures of products. We finally found that the desired elimination to **16** could be achieved by using the dialkoxydiarylsulfurane **20**[17] (CCl$_4$, 25 °C, 81% yield), a reagent described by Martin[18] for E$_2$ β-elimination of alcohols.

The 5*E* dienoic ester **16** was then converted to the corresponding 5*Z* isomer **17** via triplet-sensitized photoisomerization. We found that sensitizers having energy of 50–55 kcal/mol can induce a virtually complete conversion of **16** to **17** [Hanovia 450-W medium-pressure UV lamp with uranium glass filter, fluorenone (E_T = 53 kcal/mol), hexane/THF, 25 °C, 88% yield]. Reduction with diisobutylaluminum hydride (toluene, −78 °C) cleanly afforded the allylic alcohol **18** (94% yield), which was then converted to the corresponding allylic chloride **19** (NCS/DMF, CH$_2$Cl$_2$, 0 °C, 95% yield).[19] Finally, treatment with lithium diphenylphosphide[20] (THF, −60 °C) followed by oxidation[21] (5% H$_2$O$_2$/H$_2$O, CH$_2$Cl$_2$, 25 °C, 93% yield) gave the desired phosphine oxide **6** ($[\alpha]^{25}{}_D$ −2.3 (c 0.5, EtOH); NMR (CDCl$_3$) δ 0.04 (12 H, 4 s), 0.84 (9 H, s), 0.90 (9 H, s), 3.19 (1 H, dt, J_1 = 8.5 Hz, J_2 = 16.0 Hz), 3.41 (1 H, dt, J_1 = 9.0 Hz, J_2 = 16.0 Hz), 4.15 (1 H, br s), 4.39 (1 H, m), 4.77 (1 H, br s), 5.15 (1 H, br s), 5.34 (1 H, q, J = 9.0 Hz).

The asymmetrically synthesized[22] keto acid **21** (Scheme II) was used as starting material for the preparation of synthon **5**. Formation of the 8α-acetoxy-17-keto intermediate **29** was effected by the following reaction sequence. The starting compound **21** was hydrogenated stereospecifically[23] to the corresponding *trans*-hydrindane derivative (H$_2$, Pd/BaSO$_4$, EtOH), which was immediately reduced to the hydroxy acid **22** (NaBH$_4$, EtOH, 72% yield from **21**). Treatment with excess of methyllithium[24] (Et$_2$O, THF, reflux, 96% yield) smoothly converted **22** to the methyl ketone **23**, which underwent mesylation (MeSO$_2$Cl, pyridine, 0 °C) to **24** and elimination to **25** (NaI, DMF, pyridine, 100 °C, 86% yield from **23**). Catalytic hydrogenation (Pd/C, EtOH, 25 °C) afforded a mixture of saturated ketones, epimeric at C$_8$, which on treatment with base (EtONa, EtOH, 25 °C) was completely converted to the more stable equatorial isomer **26** (96% overall yield). Baeyer–Villiger oxidation (m-CPBA, CH$_2$Cl$_2$, 25 °C, 95% yield) transformed **26** to **27**. The *tert*-butyl group of **27** was selectively removed on treatment with trimethylsilyl iodide[25] (CCl$_4$,

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25 °C, 98% yield), and the product **28** was oxidized[26] to the corresponding ketone **29** (PCC, CH_2Cl_2, 25 °C, 95% yield).

The 25-hydroxy side chain with proper absolute stereochemistry at C-20 was then introduced by the use of the recently disclosed ene reaction.[27] Compound **30**, obtained by saponification of **29** (EtONa, EtOH, 25 °C), was subjected to Wittig reaction with ethylidenetriphenylphosphorane (THF, 25 °C) to give a 96:4 ratio (determined by GLC) of the desired 17*Z* olefin **31** and the corresponding 17*E* isomer. Since the two isomers could not be separated at this stage, they were acetylated (Ac_2O, pyridine, 25 °C, 96% yield) and the resulting acetates (mainly containing **32**) subjected to ene reaction with ethyl propiolate[27] ($EtAlCl_2$, CH_2Cl_2, 25 °C, 88% yield). We found that **32** reacted under these conditions at a considerably faster rate than the corresponding 17*E* isomer, allowing, therefore, dienoic ester **33** to be obtained virtually as single product. Catalytic hydrogenation of **33** proceeded stereospecifically to **34** (H_2, Pd/C, EtOH, 25 °C, 98% yield), and subsequent reduction with diisobutylaluminum hydride (CH_2Cl_2, toluene, −78 °C, 92% yield) gave the aldehyde **35**, which was converted to the olefin **36** with isopropylidenetriphenylphosphorane (THF, 25 °C, 89% yield). Oxymercuration and demercuration of **36** [$Hg(OAc)_2$, THF, H_2O, then $NaBH_4$, 25 °C] followed by oxidation[26] (PCC, CH_2Cl_2, 25 °C, 78% yield from **36**) afforded finally the desired hydroxylated Windaus and Grundmann ketone **5**,[28] identical in all respects with the compound prepared by ozonolysis of 25-hydroxycholecalciferol;[29] $[\alpha]^{25}{}_D$ +17.9 (*c* 0.5, EtOH); NMR ($CDCl_3$) δ 0.64 (3 H, s), 0.97 (3 H, d, $J = 6.0$ Hz), 1.22 (6 H, s).

With **5** and **6** in hand, the stage was set for the final convergent formation of 1α,25-dihydroxycholecalciferol (**1**). Wittig–Horner reaction at low temperature of **5** with excess of the lithium phosphinoxy carbanion prepared from **6** and butyllithium at −78 °C[5] in tetrahydrofuran proceeded exceedingly slow. At higher temperature, epimerization of **5** at C-14 began to occur. Much better results were obtained after protection of the hydroxy group of **5** (TMSI, THF, 25 °C, 98% yield). The trimethylsilyl ether obtained underwent Wittig–Horner reaction very smoothly (THF, −78 °C, 1 h) to give, after removal of the silyl groups[30] [$(Bu)_4NF$, THF, 25 °C], the desired 1α,25-dihydroxycholecalciferol **1**[31] in 87% yield from **5**: mp 118–119 °C; $[\alpha]^{25}{}_D$ +47.9 (*c* 0.3, EtOH); NMR[32] (CD_3OD) δ 0.57 (3 H, s), 0.96 (3 H, d, $J = 6.0$ Hz), 1.16 (6 H, s), 4.87 (1 H, br s), 5.28 (1 H, br s), 6.08 (1 H, d, $J = 11.6$ Hz), 6.32 (1 H, d, $J = 11.6$ Hz).

Acknowledgment. We thank the staff of the physical chemistry department of Hoffmann-La Roche Inc. for the determination of physical and analytical data, particularly Dr. J. F. Blount, who carried out the X-ray structure determination.

Registry No. 1, 32222-06-3; **5**, 70550-73-1; **6**, 81522-68-1; **7**, 2244-16-8; **8**, 39903-97-4; (*E*)-**9**, 81570-18-5; (*Z*)-**9**, 81570-19-6; **10**, 81506-17-4; **11**, 81506-18-5; **12**, 81506-19-6; **13**, 81506-20-9; **14**, 81506-21-0; **15**, 81506-22-1; **16**, 81506-23-2; **17**, 81570-20-9; **18**, 81506-24-3; **19**, 81506-25-4; **21**, 31944-51-1; **22**, 81506-26-5; **23**, 81506-27-6; **24**, 81506-28-7; **25**, 81506-29-8; **26**, 81506-30-1; **27**, 81506-31-2; **28**, 81506-32-3; **29**, 81506-33-4; **30**, 81506-34-5; (*E*)-**31**, 81506-35-6; **32**, 81506-36-7; **33**, 81506-37-8; **34**, 81506-38-9; **35**, 81506-39-0; **36**, 81506-40-3; **5** TMS ether, 81506-41-4; (*Z*)-**31**, 81506-42-5.

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^{127}I-Plasma Desorption Mass Spectrometry of Insulin

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We report the first observation of the molecular ion of insulin in a mass spectrum. Using a beam of 90-MeV ^{127}I ions directed on the surface of a thin film of bovine insulin, we have been able to desorb and detect the molecular ion plus prominent fragment ions relating to the α and β chain of insulin. To our knowledge, this is the largest naturally occurring peptide for which it has been possible to detect the molecular ion by a mass spectrometric method.

Since the introduction of ^{252}Cf-plasma desorption mass spectrometry (^{252}Cf-PDMS), which utilizes the 80–100-MeV fission fragment ions (M = 100–140) from a ^{252}Cf source to induce ion desorption from thin films,[1] it has been suggested that heavy ions from a nuclear accelerator in the same mass–energy domain could also produce the short-lived, high-temperature tracks in thin dielectrics that are responsible for ion desorption. The efficacy of ^{252}Cf-PDMS in desorbing large biomolecules such as β-endorphin[2] and synthetic protected oligonucleotides[3] has already been demonstrated. The most important properties of the incident ion for enhanced desorption are mass, energy, and atomic charge state.[4] The 90-MeV ^{127}I (+20 charge state) beam from the Uppsala Tandem Accelerator was chosen for this study. Since the mechanism for desorption and ionization is the same as for ^{252}Cf fission fragments, we shall refer to this method as ^{127}I-plasma desorption mass spectrometry (^{127}I-PDMS).

A thin film of bovine insulin (Sigma) was prepared by electrospraying[5] a solution in trifluoroacetic acid onto a thin aluminized Mylar film (1.5 μm thick, Steiner Film Corp.). The deposit weighed 25 μg spread over an area of 80 mm^2. The sample film was mounted in the ion source of a specially designed time-of-flight (TOF) mass spectrometer having a field-free length of 35 cm.[4] The detection of each transmitted ion initiated a mass scan covering a range of m/z 0–12 000. The sample foil was maintained at a 20-kV potential, and ions desorbed from the surface of the sample with the same polarity as the target voltage were accelerated to ground potential through a 90% transmission Ni grid. These were transmitted to the end of the flight tube where they were detected by using microchannel plate electron multipliers (Galileo Electro-Optics). The time intervals between the detection of a ^{127}I ion passing through the target and ions arriving at the end of the flight tube were measured by using a time-to-amplitude converter (TAC). The ouput of the TAC was fed directly into

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