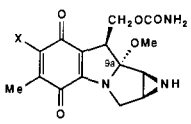
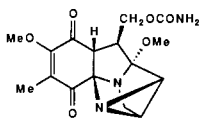
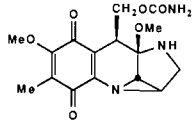


1: X = NH_2 Mitomycin C
2: X = OMe Mitomycin A



3: Aibomitomycin A



4: Isomitomycin A

is known to produce mitomycins.[6] They also found an astonishing fact that **2**, **3**, and **4** form an equilibrium mixture in which mitomycin A (**2**) is the heavily favored isomer.[7] These exciting findings suggest that isomitomycin A (**4**) is a synthetic equivalent of mitomycin C (**1**). In this communication we report a highly efficient total synthesis of racemic isomitomycin A (**4**), which paves the way for a practical synthesis of mitomycins.

Treatment of a mixture of the readily available chalcone **5**[8] and the furan **6**[9] in CH_2Cl_2 with 0.1 equiv of $SnCl_4$ at −78 °C gave, upon acidic workup, the adduct **7** in 98% yield[10] (Scheme I). The azido butenolide **7** underwent facile intramolecular azide–olefin cycloaddition[11] to give exclusively the tetracyclic aziridine **8** (toluene, 110 °C, 2 h, 93%). The stereochemistry of the side chain of **8** was confirmed by extensive NOE studies. Aminolysis of the strained lactone **8** with 1.6 equiv of 3-(3,4-dimethoxybenzyloxy)propylamine (**9**)[12] furnished directly the hydroxy lactam **10** (CH_2Cl_2, 40 °C, 1 h, 87%), whose hydroxy group was subsequently methylated to give the ether **11** (MeI, *t*-BuOK/*t*-BuOH, THF, room temperature, 79%). Manipulation of the side chain was performed in the following manner. The ketone **11** was converted to the olefin **12** in 77% yield in a three-step sequence ((1) $NaBH_4$, MeOH, room temperature; (2) $SOCl_2$, 2,6-lutidine, CH_2Cl_2, room temperature; (3) LiBr, DBU, DMSO, 80 °C). Ozonolysis of the olefin **12** (MeOH, −78 °C) and subsequent reduction with $NaBH_4$ afforded the alcohol **13**. The alcohol **13** was converted to the carbamate **14** in the conventional manner ((1) $ClCO_2Ph$, pyridine, room temperature; (2) NH_3, MeOH, room temperature, 80%). Since our model studies had revealed unusual instability of the isomitomycin A system under acidic conditions, it was necessary to deprotect the veratryl ether **14** at this stage under mild conditions to give the alcohol **15** (DDQ, H_2O, CH_2Cl_2, room temperature, 97%).[13] Reduction of the lactam **15** to the amine **17** was achieved in 68% yield via oxazine **16** through a one-pot, two-stage sequence ((1) DIBAL, THF, room temperature; (2) $NaBH_3CN$, MeOH, THF, room temperature). Hydrogenolysis of the phenolic benzyl ether **17** (H_2 (1 atm), 10% Pd/C, EtOH, room temperature) followed by oxidation with DDQ (H_2O, DMSO, acetone, −78 °C) furnished the desired *p*-quinone **18** in 77% yield. Finally, deprotection of the propanol group was achieved in the following manner. Swern oxidation[14] of the alcohol **18** gave the aldehyde **19** in 90% yield. The aldehyde **19** underwent the retro-Michael reaction upon treatment with pyrrolidine (5 equiv) and acetic acid (10 equiv) in CH_2Cl_2 at room temperature, giving isomitomycin A (**4**) in 70% yield.[15] The synthetic isomitomycin was identical with an authentic sample in TLC behavior and spectroscopic properties.[16] Equilibration of synthetic **4** ($Al(O\text{-}i\text{-}Pr)_3$, MeOH, room temperature, 2 days) furnished mitomycin A (**2**) in 91% yield, which was subsequently converted to mitomycin C (**1**) by ammonolysis in MeOH.[17]

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Supplementary Material Available: NMR spectra of key intermediates and synthetic isomitomycin A (5 pages). Ordering information is given on any current masthead page.

(6) (a) Kono, M.; Saitoh, Y.; Shirahata, K.; Arai, Y.; Ishii, S.; Morimoto, M.; Ashizawa, T. Presented at the 27th Symposium on the Chemistry of Natural Products, Hiroshima, Japan, October 1985, Abstracts, pp 672–679. (b) Kono, M.; Saitoh, Y.; Shirahata, K.; Arai, Y.; Ishii, S. *J. Am. Chem. Soc.* **1987**, *109*, 7224.

(7) This reaction was named as "Mitomycin Rearrangement".

(8) Fukuyama, T.; Yang, L.-H. *Tetrahedron Lett.* **1986**, *27*, 6299. This compound can now be synthesized from commercially available 2,6-dimethoxytoluene in 64% overall yield.

(9) Prepared from readily available 5-ethylthiobutenolide in 77% yield (Me_3SiCl, Et_3N, $ZnCl_2$, acetonitrile, room temperature).

(10) Although we do not have a direct evidence, this unusually high stereoselectivity might be attributable to the Lewis acid-promoted Diels–Alder reaction through endo addition.

(11) Smith, P. A. S.; Chou, S.-S. P. *J. Org. Chem.* **1981**, *46*, 3970.

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(16) We are indebted to Drs. T. Hirata and K. Shirahata, Kyowa Hakko Kogyo Co., Ltd., Tokyo, for a sample of authentic isomitomycin A.

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Solid-Phase Peptide Synthesis Using a Cobalt(III) Spacer between the Resin and the Peptide

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One of the most important steps in the successful synthesis of peptides using solid phase peptide synthesis (SPPS) is the attachment of the first amino acid to the solid support.[1] This is usually accomplished by using any number of spacer groups which have been developed recently for attaching amino acid derivatives to the solid support.[2,12] Among the available spacer groups the benzyl ester linkage of Boc-amino acids is still the most widely used spacer.[1,3] The disadvantage of this spacer is that removal of a peptide from this resin requires the use of liquid HF or other strongly acidic media (e.g., HBr in trifluoroacetic acid), does not allow the removal of protected peptides, and frequently results in lower peptide yields.[3]

In this communication we describe novel chemistry leading to the synthesis of a new spacer for the attachment of amino acids to solid supports used in SPPS. We have extended the solution phase peptide methodology with cobalt(III) protecting groups[6-10] to solid phase peptide methodology. The advantage of using this new spacer is the ready removal of the synthesized peptides, including protected peptides, under very mild conditions and in high yield. This new spacer is based on bis(ethylenediamine)cobalt(III) chemistry.[4,5] With use of the newly synthesized

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(6) Similar pentaammine cobalt(III) complexes were used in our laboratory as C-terminal protecting groups for the synthesis of peptides in solution.[7-10]

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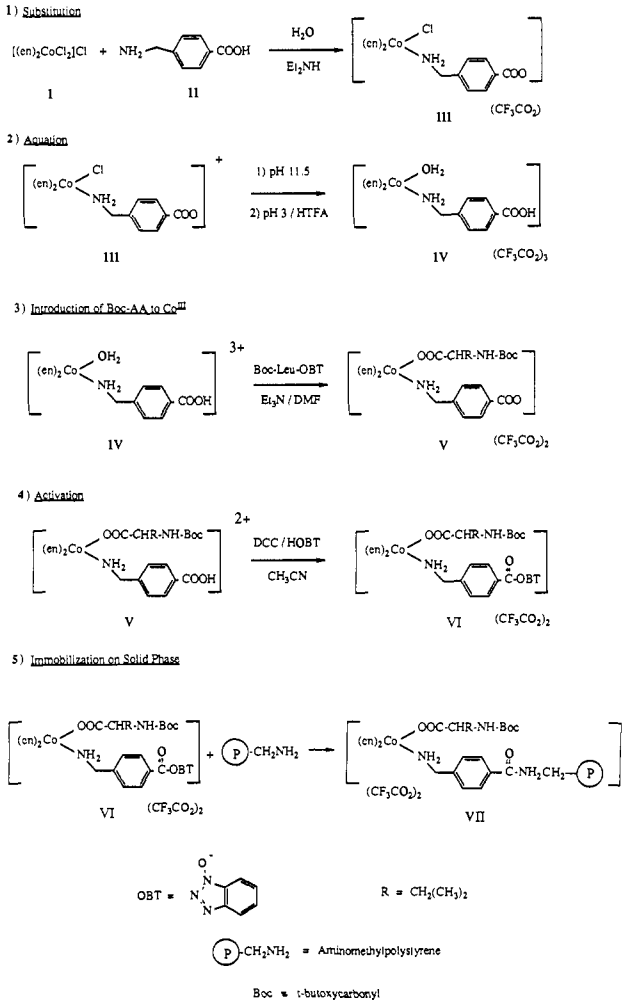
Scheme I. Immobilization of Cobalt(III) Complexes on Polystyrene Resins



cobalt(III) anchored amino acid resin to be described here, stepwise peptide synthesis can be carried out with the same reagents and techniques used in conventional SPPS.[1]

Scheme I outlines the steps involved in the successful, *quantitative* immobilization of cobalt(III) on a polystyrene resin. The scheme to be described was developed after a variety of other unsuccessful approaches were attempted. These earlier unsuccessful approaches had in common carrying out reactions on cobalt(III) centers already immobilized on the resin. In contrast, in the successful strategy all the cobalt(III) reactions prior to the final resin attachment step were carried out in solution. This enabled us to characterize and purify all the cobalt(III) intermediates in solution prior to the immobilization step.

Starting with $[(en)_2CoCl_2]Cl$ (Scheme I), where en = $NH_2CH_2CH_2NH_2$, substitution of 4-(aminomethyl)benzoic acid (4AMB) for one chloride is carried out in aqueous organic base. Aquation of the second chloride results in the formation of IV. Compound IV undergoes a general reaction with any activated Boc-amino acid active ester to produce V. Compound V is then activated at the carboxylic acid end to produce the active ester VI. In the final step compound VI can be added directly to (aminomethyl)polystyrene[11] to produce VII, a polystyrene resin with a cobalt(III) complex attached to the first amino acid of the peptide to be synthesized.

The coupling of the cobalt complex VI to (aminomethyl)-polystyrene in step 5 proceeded quantitatively as evidenced by amino acid analysis of the bound leucine. In the present work, the cobalt–leucine complex was used; however, cobalt complexes of a variety of other Boc-amino acids have been reported in earlier publications.[6,7]

Scheme II

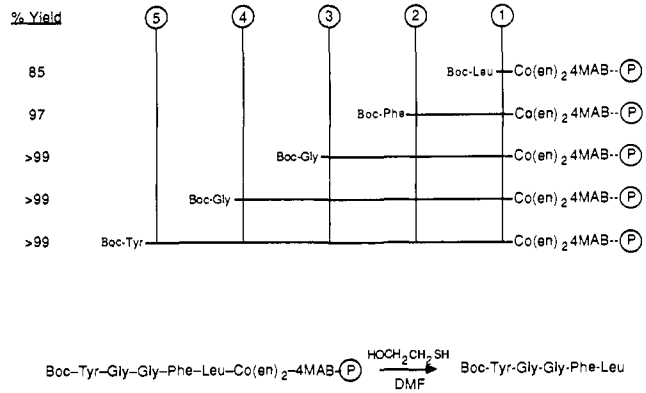


Table I. Amino Acid Analysis of Intermediate Resin Peptides from the Leu-Enkephalin Synthesis

peptides	ratio of amino acids
Leu-Phe	1.00:0.97
Leu-Phe-Gly	1.00:0.98:1.05
Leu-Phe-Gly-Gly	1.00:1.08:2.15
Leu-Phe-Gly-Gly-Tyr	1.00:1.02:2.04:1.23[a]

[a] Reference 13.

In this communication we have used the cobalt(III) resin for the synthesis of the pentapeptide Leu-enkephalin. Starting with the cobalt resin VII (0.37 mmol Leu/g resin), stepwise peptide synthesis was carried out by using standard procedures for solid phase synthesis[3] (Scheme II). During this synthesis all the intermediate peptides on the cobalt resin were subjected to amino acid analysis (Table I). In some cases the protected peptide intermediates also were removed from the resin by treatment with mercaptoethanol in DMF (1M) for several minutes and then separately analyzed for their amino acid content. At the end of the synthesis the resulting protected pentapeptide was removed from the resin by treatment of the resin with mercaptoethanol in DMF (1M) and was purified by gel filtration and RP-HPLC. The peptide was then deprotected (with use of CF_3COOH/CH_2Cl_2) and analyzed by RP-HPLC and amino acid analysis.[14] The retention time of the synthesized peptide was also compared to that of an authentic sample.

Experiments to determine the stability of the cobalt peptide linkage on the resin have shown that this linkage is extremely stable. When the cobalt resin VII was left in contact with 50% CF_3COOH/CH_2Cl_2 for 72 h, only 3.1% of the bound leucine was removed.

In summary, the cobalt(III) spacer on (aminomethyl)polystyrene described here offers all the advantages of solid phase peptide synthesis, combined with ease of removal of the synthesized peptide. The benefit of a cobalt(III) spacer over all the commonly used organic spacers is that it also allows the removal of *protected* peptides from the resin, which can then be used for the synthesis of very large peptides by the technique of fragment condensation.

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(14) The reaction of 2-mercaptoethanol with the cobalt spacer is expected to be quantitative; however, the cleavage of Boc-Leu-enkephalin from the resin with use of 2-mercaptoethanol in DMF resulted in the isolation of only 73% of crude protected peptide and 51% isolated pure protected peptide. Higher yields of the peptide were obtained when more elaborate methods for extraction of the peptide from the resin were used (ref 3).

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Effective Photoreduction of CO_2/HCO_3^- to Formate Using Visible Light

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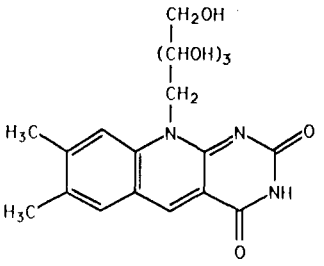
Photoreduction of CO_2 and its aqueous forms to organic products is a challenging subject as a means of mimicking photosynthesis and solar energy conversion and storage.[1,2] Photoreduction of CO_2 to formate has been reported with use of homogeneous catalysts,[3] semiconductor powders[4] or electrodes,[5] and the enzyme formate dehydrogenase.[6] Recently, we were able to photoreduce CO_2 to methane,[7] although in low yields. Electrocatalyzed reductions of CO_2 have been extensively studied,[8,9] but these do not occur at the thermodynamic potential for formate formation. Wrighton et al. have examined[10] the reduction of HCO_3^- to formate by hydrogen and the electroreduction of HCO_3^-, in the presence of various supported palladium catalysts, in which effective formate production has been accomplished at room temperature close to the thermodynamic potential. Interestingly, the photosensitized reduction of CO_2/HCO_3^- using Pd-based heterogeneous catalysts has not been reported. Here we wish to report on the design of a novel heterogeneous Pd colloid stabilized by β-cyclodextrin (β-CD)[11] and its application in the effective reduction of CO_2/HCO_3^- to formate. High quantum yields, ϕ = 1.1 are reported for formate production. We find that the β-CD support strongly affects the catalyst activity.

Photoreduction of *N,N'*-dimethyl-4,4'-bipyridinium salt, methyl viologen, MV^{2+}, with various sensitizers and sacrificial electron donors, has been extensively explored in recent years.[12,13] Krasna has found[14] that deazariboflavin, dRFl (**1**), acts as an effective



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photosensitizer for the reduction of MV^{2+}. For example, in the presence of oxalate as electron donor, $MV^{\bullet+}$ is photogenerated in quantum yields $\phi > 1$. Comparison of the reduction potential of $MV^{\bullet+}$ ($E°(MV^{2+}/MV^{\bullet+})$ = -0.45 V vs NHE[15]) to the thermodynamic potential for formate formation ($E°(HCO_3^-/HCO_2^-)$ = -0.42 V vs NHE,[16] at pH 7) suggests that the thermodynamic balance for the process outlined in eq 1 corresponds to $\Delta G° \approx$

$$2MV^{\bullet+} + HCO_3^- + 2H^+ \rightleftharpoons 2MV^{2+} + HCO_2^- + H_2O \quad (1)$$

0. ıus, by the light-driven generation of $MV^{\bullet+}$ high concen- t s of formate could, in principle, be accumulated. Yet, this is kinetically unfavored, and no formate is formed in that include CO_2/HCO_3^- and photogenerated $MV^{\bullet+}$. ind that Pd supported on β-CD acts as an effective catalyst photoreduction of CO_2/HCO_3^-, by $MV^{\bullet+}$. The system ıposed of an aqueous sodium bicarbonate solution (3 mL), , that included deazariboflavin, dRFl (**1**), as photosensitizer, $^{-5}$ M, MV^{2+}, 2×10^{-3} M, as primary electron acceptor, ai. xalate as sacrificial electron donor, 0.06 M. Pd-β-CD colloid (30 mg·L^{-1}) was added to the solution, and CO_2 was bubbled through the system (final pH 6.8). Illumination of the system ($\lambda > 400$ nm), at 30 °C, results in the formation of formate, HCO_2^-, and trace amounts of hydrogen. Figure 1 shows the rate of HCO_2^- and H_2 formation at time intervals of illumination.[17] The quantum yields correspond to $\phi(HCO_2^-)$ = 1.1 and $\phi(H_2)$ = 0.03. Control experiments reveal that in the absence of CO_2/HCO_3^- the major photoproduct is H_2 (eq 2), ϕ = 0.12, and

$$2MV^{\bullet+} + 2H^+ \xrightarrow{\text{Pd-}\beta\text{-CD}} 2MV^{2+} + H_2 \quad (2)$$

only trace amounts of HCO_2^- are formed by in situ generation of CO_2 by the oxidation of oxalate (vide infra). Also, in the absence of the Pd-β-CD colloid no HCO_2^- or H_2 are produced, and $MV^{\bullet+}$ is the only photoproduct, $\phi(MV^{\bullet+}) \approx 3.5$. Illumination of an aqueous system that includes dRFl (**1**), MV^{2+} as electron acceptor, oxalate as electron donor, and a Pt colloid stabilized by β-CD results in the formation of H_2, and no formate is formed. These results clearly indicate that formate is not formed by the sacrificial oxidation of oxalate and that Pd-β-CD is a specific catalyst for the photoreduction of CO_2/HCO_3^- to formate.[18] Comparison of the amount of photogenerated formate to the

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(11) The colloid of Pd stabilized by β-CD was prepared by heating a 1.5 $\times 10^{-3}$ M $PdCl_4^{2-}$ solution that included β-CD (1% w/w) at 70 °C for several minutes till the color changed. Heating was continued another 2-3 min. The colloid was then deionized (with Amberlite MB-1) and centrifugated (5000 rpm, 30 min). The mean particle diameter of the colloid was estimated to be 150 Å by electron microscopy measurements. Preparation of metal colloids stabilized by cyclodextrins has been previously reported. Cf. Komiyama M.; Hirai, H. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 2833.

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(18) At pH ≤ 5 no formate is photogenerated, and the only photoproduct is H_2. This suggests that HCO_3^- is the substrate being reduced to formate rather than CO_2. In the specified systems, pH 6.8, CO_2 is included to maintain constant pH and HCO_3^- concentration.

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